

## THE ROLE OF INSTITUTIONAL REVIEW BOARDS IN PROTECTING HUMAN SUBJECTS: ARE WE REALLY READY TO FIX A BROKEN SYSTEM?

*Hazel Glenn Beh\**

### I. INTRODUCTION

The history of human subject research has been characterized “as one of ‘progress propelled by scandal.’”<sup>1</sup> This depiction seems accurate in light of past research atrocities in modern history including the Tuskegee Syphilis Study conducted from 1932 until 1972, the intentional exposure of soldiers and Navaho miners to radiation in the 1940s and 1950s, the LSD experiments secretly conducted on American soldiers by the Army and the CIA in the 1950s and 1960s, the Japanese military’s “plague bomb” experiments during World War II, and the typhus experiments conducted at Buchenwald concentration camp. Although such abuses were thought to be relegated to the past, recent research tragedies have again focused the spotlight on human subject research.

The Court of Appeals of Maryland recently issued the landmark decision of *Grimes v. Kennedy Krieger Institute, Inc.*,<sup>2</sup> involving human subject research on children, which has shaken the research community.

---

\* Hazel Glenn Beh is an Associate Professor with the William S. Richardson School of Law at the University of Hawaii, a hospital Institutional Review Board member, and a former vice-chair and member of the University of Hawaii’s Institutional Review Board. J.D. 1991, University of Hawaii; Ph.D. 1985, University of Hawaii; M.S.W. 1975, University of Hawaii; B.A. 1973, University of Arizona. The author thanks Rebecca Ohta and William Dendle for their invaluable insights.

1. Mary R. Anderlik & Nanette Elster, *Lawsuits Against IRBs: Accountability or Incongruity?*, 29 J.L. MED. & ETHICS 220, 222 (2001) (quoting Ruth Faden & Tom Beauchamp, *Removing ‘Deficiencies’ in Human Research*, BALTIMORE SUN, Mar. 5, 2000, at C3).

2. 782 A.2d 807 (Md. 2001).

The court reversed a grant of summary judgment in favor of Kennedy Krieger Institute, an affiliate of the prestigious Johns Hopkins University, and remanded the case for trial to consider whether it was liable to low-income children and their families who participated as human subjects in a lead paint poisoning study it conducted.<sup>3</sup> This decision went much further, however, and the vastness of the court's rulings will likely force all researchers and Institutional Review Boards (IRBs)<sup>4</sup> involved in human subject research to take note.

The court's comments about the research design were unrestrained and must have surely embarrassed and stung Kennedy Krieger, the Johns Hopkins Institutional Review Board, and the particular researchers involved. For example, the court noted that because this study involved experiments on vulnerable subjects, it "present[ed] similar problems" but differed significantly from some of the most notorious and egregious instances of human subject research abuses in modern history.<sup>5</sup> Yet, however large the dissimilarities, modern research institutions do not want to be included in such a list of research atrocities.<sup>6</sup> In response to the court's comparison, which was "widely repeated in the local and national press,"<sup>7</sup> Kennedy Krieger complained:

The resulting firestorm of criticism, shock, embarrassment, and inflammatory publicity in the public press has been enormously unfair to an institution with an outstanding record dedicated to helping children, especially poor children, with serious medical problems. What Kennedy Krieger and its dedicated scientists sought to do here bears no resemblance whatsoever to the atrocious examples of study participants being affirmatively poisoned and/or intentionally deceived about the availability and appropriateness of medical attention.<sup>8</sup>

Kennedy Krieger is not the sole institution facing criticism regarding

---

3. *Id.*

4. Established by the federal system, these boards were created and designed solely to protect human subjects from research abuse by ensuring that the research was ethically designed to include minimal risks and fairly balanced with potential benefits as well as to guarantee that subject participation is informed and voluntary. *Id.* at 813.

5. *Id.* at 816-17 (mentioning the Tuskegee Syphilis Study, the radiation studies, the LSD experiments, the Japanese military's "plague bomb" studies, and the typhus experiments conducted at Buchenwald concentration camp).

6. A concurring judge distanced herself from the court's resolution of issues beyond the scope of the question presented and the court's adoption of the Nuremberg Code into state law and declined to "join in the majority's comparisons between the research at issue in [the] case and extreme historical abuses, such as those of the Nazis or the Tuskegee Syphilis Study." *Id.* at 858-61 (Raker, J., concurring in result only).

7. *Grimes v. Kennedy Krieger Inst., Inc.*, Appellee's Motion for Partial Reconsideration and Modification of Opinion, (Sept. 17, 2001), available at <http://www.hopkinsmedicine.org/press/2001/SEPTEMBER/kennedykriegermotion.htm>

8. *Id.*

research abuse involving human subjects. In fact, as a result of recent, well-publicized incidents that led to the deaths of several human subjects, there is plenty of embarrassment to go around in the scientific community.<sup>9</sup> Because much of the criticism arising from these recent scandals has been lodged not only against the researchers but also against the local Institutional Review Boards that approved the research initially, national attention has highlighted the failings of these boards that were designed to protect human subjects.

By analyzing the impact of the *Grimes* decision and evaluating the current problems underlying the IRB system as well as the federal regulations designed to protect research subjects, the Article demonstrates the need for immediate reform. Part II discusses *Grimes*, looking at the court's description of the protocol, the consent process, and the perceived flaws in each, as well as its harsh criticism directed at the IRB. Although the case has been remanded,<sup>10</sup> the court's commentary regarding human subject research, particularly the involvement of children in such research, is landmark. More importantly, the court carved out a significant and long-neglected judicial role in the oversight of this form of research. In Part III, the Article outlines the responsibilities of IRBs under the federal system and addresses how they protect subjects from unethical research. By describing a few ethical lapses that have recently occurred at several prestigious institutions, Part IV suggests that IRBs have failed to adequately protect human subjects. While Part V discusses the growing criticism that the current system designed to protect human subjects is broken and in need of substantial reform, Part VI comments on the recent recommendations for reform issued by the National Bioethics Advisory Commission. Among its many recommendations, the blue ribbon panel suggested more independent methods of review, increased guidance, education, and resources directed toward the IRB system, as well as the implementation of certification and accreditation systems.<sup>11</sup> The Article concludes by noting that reforms are no longer the sole jurisdiction of federal policy makers. As *Grimes* and the spate of recent lawsuits against other research institutions have made clear, reform will come, if not by legislation and rulemaking, then by judicial fiat.

---

9. See discussion *infra* Part IV.

10. *Grimes*, 782 A.2d at 861.

11. NATIONAL BIOETHICS ADVISORY COMMISSION, ETHICAL AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS vii (Aug. 2001), available at <http://bioethics.georgetown.edu/nbac/human/overvol1.pdf> [hereinafter NBAC, ETHICAL AND POLICY ISSUES].

## II. *GRIMES V. KENNEDY KRIEGER INSTITUTE, INC.*

In 1993, the Environmental Protection Agency awarded a research study grant to Kennedy Krieger Institute, a well-regarded research institution affiliated with Johns Hopkins University.<sup>12</sup> Entitled "Evaluation of Efficacy of Residential Lead Based Paint Repair and Maintenance Interventions," the purpose of the study was "to characterize and compare the short and long-term efficacy of comprehensive lead-paint abatement and less costly and potentially more cost-effective Repair and Maintenance interventions for reducing levels of lead in residential house dust which in turn should reduce lead in children's blood."<sup>13</sup>

### A. *The Study Design*

Lead paint poses health risks to humans and to children in particular since exposure impairs the cognitive and physical development of young children.<sup>14</sup> Lead poisoning affects nearly one million children in the United States,<sup>15</sup> and in fact, lead paint toxicity constitutes "one of the top environmental hazards facing children under age six."<sup>16</sup> Because minority and poor children tend to reside in older, poorly maintained homes built prior to 1978,<sup>17</sup> they are especially vulnerable.<sup>18</sup> As paint deteriorates, "it chips and peels, making it easily accessible for children to chew and to ingest . . . [and] create[s] lead dust that will deposit on a child's toys, hands, or food."<sup>19</sup>

Completely eradicating lead paint from contaminated rental units is extremely costly.<sup>20</sup> Thus, because landlords face potential civil liability for renting houses contaminated with lead,<sup>21</sup> in some instances, they decide simply to abandon the property, leaving it vacant rather than under-

---

12. *Grimes*, 782 A.2d at 819.

13. *Id.* (internal quotation marks omitted).

14. *Id.* ("Lead poisoning poses a distinct danger to young children. It adversely affects cognitive development, growth, and behavior. Extremely high levels have been known to result in seizures, coma, and even death.") (internal quotation marks omitted).

15. Kara Kurtzman Daghljan, *Lead-Based Paint: The Crisis Still Facing Our Nation's Poor and Minority Children*, 9 DICK. J. ENVTL. L. & POL'Y 535, 535 (2001) (citing Hous. and Urban Dev., at <http://www.hud.gov:80/lea/leapboff.html#serious>).

16. *Id.* at 536.

17. The use of lead paint in homes was prohibited in 1978. Verne A. Pedro, Note, *Still Hazy After All These Years: New York City's Local Law 38 and the Legislative Debate over Landlord Liability in Lead Paint Poisoning Cases*, 24 SETON HALL LEGIS. J. 541, 554 (2000).

18. Daghljan, *supra* note 15, at 538.

19. *Id.* at 538-39.

20. *Grimes*, 782 A.2d at 821.

21. To understand the development of landlord tort liability for lead paint poisoning in Maryland courts, see *Brown v. Dermer*, 744 A.2d 47 (Md. 2000); *Richwind Joint Venture 4 v. Brunson*, 645 A.2d 1147 (Md. 1994); *Scroggins v. Dahne*, 645 A.2d 1160 (Md. 1994); *Bartholomee v. Casey*, 651 A.2d 908 (Md. Ct. Spec. App. 1994).

take expensive rehabilitation efforts.<sup>22</sup> Despite the dangers associated with lead paint, federal laws aimed at reducing contamination in older homes have not been altogether successful in decreasing exposure.<sup>23</sup> In addition to lead paint dust in older homes caused by flaking paint, children face other exposure because lead may be concentrated in soil, pipes, and solder.<sup>24</sup>

In light of the large number of homes containing lead hazards, Kennedy Krieger planned a study to determine a safe and inexpensive method to remove sufficient lead so to prevent dangerous exposure to children.<sup>25</sup> The study was conducted in Baltimore and the experimental arm involved the use of older low-income rental units containing lead paint.<sup>26</sup> The study was comprised of five groups consisting of twenty-five houses each.<sup>27</sup> Under the research protocol, researchers sought houses that were "structurally sound" and that were either built prior to 1941 or "had documented lead based paint" present to qualify in the first three test groups.<sup>28</sup> Each of the first three groups of houses received grants or loans for different levels of repair and maintenance aimed at reducing lead paint.<sup>29</sup> Level one houses received \$1,650 intended to cover a "minimal level of repair and maintenance,"<sup>30</sup> Level two received \$3,500 intended to cover "a greater level of repair and maintenance,"<sup>31</sup> and Level three houses received between \$6,000 and \$7,000 to spend on "an even greater level of repair and maintenance."<sup>32</sup> Groups four and five

---

22. *Grimes*, 782 A.2d at 821.

23. *See, e.g.*, Daghljan, *supra* note 15, at 539-45 (discussing the weaknesses in federal legislation dealing with lead-based paint hazards).

24. *Id.* at 535-36.

25. *Grimes*, 782 A.2d at 819.

26. *Id.*

27. *Id.* at 820.

28. *Id.* at 822-23.

29. *Id.* Kennedy Krieger assisted landlords in applying for grants and loans for abatement. *Grimes*, 782 A.2d at 821; *see also* Daghljan, *supra* note 15, at 541-43 (describing the Residential Lead-Based Paint Hazard Reduction Act of 1992 ("Title X"), Pub. L. No. 102-550, 106 Stat. 3897, and its efforts to alleviate lead-based paint dangers through monetary grants to qualifying applicants).

30. *Grimes*, 782 A.2d at 821-22.

Repair & Maintenance Level I interventions were capped . . . at \$1,650 and included wet-scraping of peeling and flaking lead-based paint and paint of unknown composition on all interior surfaces, including walls, trim, and doors; repainting of treated surfaces; installation of window well caps; repainting of all exterior window trim, repainting of all interior window sills; vacuuming of all horizontal surfaces and window components with a high efficiency particulate (HEPA) vacuum; and wet cleaning all horizontal surfaces.

*Id.* at 822.

31. *Id.* "Level II interventions were capped . . . at \$3,500 and included all the elements of Level I intervention plus two key additional elements: use of sealants and paints to make floors smoother and more easily cleanable, and in-place window and door treatments to reduce abrasion of lead-painted surfaces." *Id.*

32. *Id.* "Level III interventions were capped . . . at \$6,000-\$7,000 and added window replacement and encapsulation of exterior door trim with aluminum, and the use of coverings on some floors and stairs to make them smooth and more easily climbable." *Grimes*, 782 A.2d at 822.

constituted control groups.<sup>33</sup> Group four consisted of houses that were already abated and received no additional repair and maintenance,<sup>34</sup> whereas Group five contained modern homes built after 1980 when lead paint was no longer used.<sup>35</sup> Of ethical significance, both vacant and occupied properties were included in the study, and vacant homes received the highest level of abatement because of the ease of abatement and repair.<sup>36</sup>

Kennedy Krieger maintained that it “knew that all three tiers of intervention reduced lead dust by approximately 80% from that found in untreated properties.”<sup>37</sup> It further asserted that “[t]he Study was designed so that every participating family in every category of housing would have the opportunity to live in safer housing than 95% of the non-lead abated housing stock in Baltimore City—and safer than required by then-federal, state or local law.”<sup>38</sup>

The human subjects enrolled in the study were the children of families that rented homes.<sup>39</sup> Notably, some children were already living in the rental units identified to the experiment, but in some instances, the families moved into the properties during the study.<sup>40</sup> The court’s decision indicates that some of the properties with lead contamination were vacant and not on the market until they became part of the study.<sup>41</sup> In fact, the landlords participating in the study actually recruited the children by consenting to allow their property to be used for the study and agreeing to attempt to rent to families with young children.<sup>42</sup> According to the court, “[t]he project required that small children be present in the

33. *Id.*

34. *Id.* The level of abatement in Groups 1 through 3 was apparently less than complete. See Appellee’s Motion for Partial Reconsideration and Modification of Opinion, *supra* note 7, at n.4.

35. *Grimes*, 782 A.2d at 822.

36. *See id.* at 821-23. As a result, it can be inferred that contaminated properties that were not on the market at the time the study began had to be placed back into the rental market. Vacant properties were more often assigned Level III or Level II abatement (2:1 ratio). *Id.* at 823 n.19. KKI explained its method for assigning abatement levels:

About half of the R&M Properties [Groups 1 through 3] were occupied before the improvements to the R&M Properties were made. The first group of homes were [sic] occupied by the same families before and after the improvements. Approximately one half of the second group of homes were [sic] occupied by the same families before and after the improvements. None of the third group of homes was [sic] occupied when the improvements were performed. The highest level of abatement was done in the third level of homes, i.e., the non-occupied residences, because vacancy allowed more abatement to be done safely.

*Lead-Based Paint Study*, available at <http://www.hopkinsmedicine.org/press/2001/SEPTEMBER/leadfactsheet.htm> (Sept. 7, 2001) [hereinafter *Lead-Based Paint Study*].

37. *Lead-Based Paint Study*, *supra* note 36.

38. *Id.*

39. *Grimes*, 782 A.2d at 821.

40. *See Lead-Based Paint Study*, *supra* note 36; *see also Grimes*, 782 A.2d at 821-23.

41. *See Grimes*, 782 A.2d at 826-27 nn.24-25.

42. *Id.* at 821.

houses. To facilitate that purpose, the landlords agreeing to permit their properties to be included in the studies were encouraged, if not required, to rent the properties to tenants who had young children.”<sup>43</sup> In return, Kennedy Krieger helped landlords apply for and receive grants or loans for lead abatement to their properties.<sup>44</sup>

Researchers recruited occupant families with at least one child between the age of five months and forty-eight months old.<sup>45</sup> Exclusion criteria included mental retardation, physical handicaps, sickle cell anemia, and likelihood of relocation prior to the study’s termination.<sup>46</sup> Parents consented on behalf of their children and agreed to submit them to blood testing as often as eight to nine times in two years, to allow their home to be tested for lead as many as eight to nine times over two years, and to answer questionnaires every six months throughout the duration of the study.<sup>47</sup> In return, the parents were paid five dollars to complete the initial questionnaire and to allow testing of the home and an additional fifteen dollars for each questionnaire that was fully completed.<sup>48</sup>

The research design required the researchers to measure lead dust levels in the houses and lead blood levels in the children over a period of two years.<sup>49</sup> Kennedy Krieger measured lead paint within the houses by utilizing an experimental method of capturing dust samples through the use of a “cyclone vacuum” as well as a traditional “dust wipe” method.<sup>50</sup> In addition, it conducted exterior soil and drinking water measurements.<sup>51</sup> Researchers also drew blood from the children involved in the study on a regular schedule and subsequently reported the results to parents.<sup>52</sup>

The Johns Hopkins University Joint Committee on Clinical Investigation, the institution’s IRB, questioned the study as first proposed.<sup>53</sup> In particular, it expressed concern that the use of healthy control children in modern urban housing was impermissible under federal regulations.<sup>54</sup> The IRB was initially concerned that the non-therapeutic use of control subjects posed a problem, and in response, it suggested changes to the consent form’s identification of benefits in order to conform to federal

---

43. *Id.*

44. *Id.*

45. *Id.* at 823.

46. *Grimes*, 782 A.2d at 823.

47. *Id.* at 824.

48. *Id.* at 824-25.

49. *Id.* at 820-21.

50. *Id.* at 828 n.26. Kennedy Krieger explained that the wipe method constitutes a recognized method of measuring lead dust, but the cyclone vacuum method had not been scientifically accepted. *Lead-Based Paint Study*, *supra* note 36.

51. *Grimes*, 782 A.2d at 822.

52. *Id.*

53. *Id.* at 814.

54. *Id.*

regulations:

The next issue has to do with drawing blood from the control population, namely children growing up in modern urban housing. Federal guidelines are really quite specific regarding using children as controls in projects in which there is no potential benefit [to the particular children]. To call a subject a normal control is to indicate that there is no real benefit to be received [by the particular children] . . . . So we think it would be much more acceptable to indicate that the "control group" is being studied to determine what exposure outside the home may play in a total lead exposure; thereby, indicating that these control individuals are gaining some benefit, namely learning whether safe housing alone is sufficient to keep the blood-lead levels in acceptable bounds. We suggest that you modify . . . consent form[s] . . . accordingly.<sup>55</sup>

The IRB eventually approved a modified consent form that reflected that all children would receive certain benefits.<sup>56</sup> After stating the level of compensation, the form explained that Kennedy Krieger agreed to "provide [the parents] with specific blood-lead results," to discuss the results of the tests performed on the house, and to explain measures that could be taken to guard against the risks of lead exposure.<sup>57</sup> Although modified, the consent form was not well drafted by any standard. For example, the benefits section identified compensation for completion of the questionnaires as a benefit.<sup>58</sup> Compensation, however, provides an incentive for participation and is not considered a benefit associated with the research.<sup>59</sup> This section also included information explaining the steps Kennedy Krieger would take to ensure privacy.<sup>60</sup> Rather than a benefit, loss of privacy constitutes a risk, and the safeguards the researchers agreed to implement to protect privacy are typically described in order to explain how that risk will be minimized.<sup>61</sup>

The court approached the case as if the research was non-therapeutic,<sup>62</sup> and its holdings and discussion flow from that assump-

---

55. *Id.* (internal quotation marks omitted).

56. *Grimes*, 782 A.2d at 824-25.

57. *Id.*

58. *Id.*

59. OFFICE FOR HUMAN RESEARCH PROTECTIONS, IRB GUIDEBOOK ch. 3 pt. A (1993), *available at* [http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter3.htm#e7](http://ohrp.osophs.dhhs.gov/irb/irb_chapter3.htm#e7) [hereinafter IRB GUIDEBOOK] ("Direct payments or other forms of remuneration offered to potential subjects as an incentive or reward for participation should not be considered a 'benefit' to be gained from research.").

60. Consent Form (on file with the author).

61. IRB GUIDEBOOK, *supra* note 59, at ch. 3 pt. G ("In behavioral, social, and some biomedical research, the methods for gathering information may pose the added risk of invasion of privacy and possible violations of confidentiality.").

62. To gain a further understanding of therapeutic as well as non-therapeutic research, *see* Charles Weijer, *The Ethical Analysis of Risk*, 28 J.L. MED. & ETHICS 344, 347 (2000); *see also*



tion.<sup>63</sup> Although the court initially stated that “there was absolutely no such [therapeutic] value of the research in respect to the minor subjects used to measure the effectiveness of the study,”<sup>64</sup> it clarified in its order denying reconsideration that “[e]very issue bearing on liability or damages remain[ed] open for further factual development,” including “whether the study in question offered some benefit, and therefore could be regarded as therapeutic in nature, or involved more than that minimal risk is open for further factual development on remand.”<sup>65</sup> Thus, on remand, the defendants may still be able to establish that all children involved in the study received therapeutic benefits.

The court harshly criticized the IRB’s involvement in labeling health monitoring as a benefit, explaining that “the IRB . . . abdicated that responsibility, instead suggesting to the researchers a way to miscast the characteristics of the study in order to avoid the responsibility inherent in non-therapeutic research involving children.”<sup>66</sup> The IRB’s comments do not indicate whether the protocol was actually changed at the suggestion of the IRB to provide education and monitoring information to the parents or whether the IRB merely suggested that the protocol identify the education and blood and house tests as benefits.

The court further concluded that the IRB “had a partial misperception of the difference between therapeutic and non-therapeutic research

---

ROBERT J. LEVINE, *ETHICS AND REGULATION OF CLINICAL RESEARCH* 6-8 (1981). Whether the therapeutic/non-therapeutic distinction is appropriate under the federal regulations or was correctly characterized in this case is subject to controversy. Loretta Kopelman, *Pediatric Research Regulations Under Legal Scrutiny: Grimes Narrows Their Interpretation*, 30 J.L. MED. & ETHICS 38, 41 (2002) (noting that many protocols have both therapeutic and non-therapeutic aspects, and therefore, the distinction is not particularly useful). The children involved in the study were theoretically “at risk” of lead exposure because they were in low-income neighborhoods in Baltimore. Ross notes that all of the subjects therefore arguably fell within the provisions of 45 C.F.R. § 46.406 and could be exposed to minor increases over minimal risks because they suffered the condition being studied, but also noting the difficulties with too broadly promoting this interpretation. Lainie Friedman Ross, *In Defense of the Hopkins Lead Abatement Studies*, 30 J.L. MED. & ETHICS 50, 53 (2002) [hereinafter Ross, *In Defense*]. Ross comments:

I am not convinced that 1) the children were healthy, as they were at serious risk for plumbism; 2) the research was non-therapeutic, as it provided lead abatement to the subjects’ homes; and 3) if the research were classified as non-therapeutic, that the research posed more than minimal risks to the children subjects. Rather, I have argued that the research was therapeutic, and that the control arm was morally permissible.

*Id.* at 53.

63. *Grimes*, 782 A.2d at 855. Kennedy Krieger denied that the research was non-therapeutic although the court disagreed. *Id.* at 839 n.32. In so doing, the court compared the research in the case *sub judice* to a study from the 1940s and 1950s in which orphan children were verbally abused and criticized to induce a stuttering disorder to prove that verbal abuse promoted stuttering: “The [researchers conducting the stuttering study], however belatedly, . . . acknowledged the impropriety of that experiment and apologized for its involvement. KKI continues to assert the propriety of a study that is inherently inappropriate—no less so than the stuttering research on vulnerable orphans in the Midwest sixty years ago.” *Id.*

64. *Id.* at 855.

65. *Id.* at 861-62.

66. *Grimes*, 782 A.2d at 813.

and the IRB's role in the process" of approving research.<sup>67</sup> It asserted that the IRB misunderstood its own role in its willingness to aid the researchers in circumventing federal regulations aimed to protect children involved in non-therapeutic research.<sup>68</sup> Moreover, the court explained that "in spite of the IRB's improper attempt to manufacture a therapeutic value, there was absolutely no such value of the research in respect to the minor subjects used to measure the effectiveness of the study."<sup>69</sup>

Although the court may have correctly recognized that the IRB misconceived the notion of benefits under the federal regulatory scheme, the concept of benefits is more complex than it appreciated.<sup>70</sup> Generally, when determining whether to approve research, federal regulations require IRBs to balance the risks and benefits to human subjects.<sup>71</sup> When the research involves children, these regulations are more stringent, requiring researchers to invoke additional protections.<sup>72</sup> When the research provides no direct benefits to the subjects and is intended to contribute to scientific knowledge in general, the researchers must closely scrutinize the risk to child subjects.<sup>73</sup> In these types of studies, IRBs may approve this research on children only after determining that the study poses no greater than minimal risks to the child.<sup>74</sup>

As one commentator explained, three possible benefits arise from re-

---

67. *Id.*

68. *Id.*; see also Kopelman, *supra* note 62, at 41 (questioning whether the non-therapeutic distinction is germane under the federal regulations).

69. *Grimes*, 782 A.2d at 855. In addition, the court stated, "the IRB, whose primary function was to insure safety and compliance with applicable regulations, encouraged the researchers to misrepresent the purpose of the research in order to bring the study under the label of 'therapeutic' and thus under a lower safety standard of regulation. The IRB's purpose was ethically wrong." *Id.* at 817. But see Ross, *In Defense*, *supra* note 62, at 52-53 (suggesting that the court may have erred in characterizing the study as non-therapeutic, and instead stating that it was a "therapeutic trial that included an ethically appropriate (minimal risk) control arm").

70. See generally, e.g., Nancy M.P. King, *Defining and Describing Benefit Appropriately in Clinical Trials*, 28 J.L. MED. & ETHICS 332 (2000) (discussing the need to properly define benefits in clinical research).

71. 45 C.F.R. § 46.111(a)(2) (2002) ("[T]he IRB shall determine that . . . [r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects . . ."). See generally King, *supra* note 70 (advocating ways to adequately inform research subjects of risks and benefits); Weijer, *supra* note 62 (discussing IRBs' roles in guarding against dangers to human research subjects).

72. See *Grimes*, 782 A.2d at 814. See generally 45 C.F.R. §§ 46.401-409 (discussing the supplementary requirements for research involving child subjects).

73. Weijer, *supra* note 62, at 349.

74. *Id.* "HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians . . ." 45 C.F.R. § 46.404. Research involving greater than minimal risk but offering the "prospect of direct benefit" is permissible only if risks and benefits are balanced, "anticipated benefit[s] to the risk[s] are] at least as favorable to the subjects as [those] presented by available alternative approaches," and guidelines are set forth for attempting to obtain adequate consent from children and parents. 45 C.F.R. § 46.405. Research presenting "an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children" but not meeting the criteria of the aforementioned categories must be approved by a panel of national experts. 45 C.F.R. § 46.407.

search including:

[D]irect benefit to subjects, which is properly defined as benefit arising from receiving the intervention being studied; collateral benefit to subjects . . . which is benefit arising from being a subject, even if one does not receive the experimental intervention (for example, a free physical exam and testing, free medical care and other extras, or the personal gratification of altruism); [and] aspirational benefit, or benefit to society and to future patients, which arises from the results of the study.<sup>75</sup>

The free blood tests, house assessments, and educational information provided to parents should be appropriately characterized as collateral or indirect benefits since they were not derived from the intervention but merely resulted from being included in the study.<sup>76</sup> Because the additional protections for children found in the regulations under Subpart D instruct IRBs to consider only direct benefits,<sup>77</sup> the presence of collateral benefits should not have changed the IRB's risk-benefit calculation.<sup>78</sup>

In *Grimes*, the benefit analysis is not simple because all of the children did not benefit to the same extent.<sup>79</sup> Some of the participants may have gained only indirect benefits, whereas others enjoyed direct benefits.<sup>80</sup> Children in groups one through three who were currently living in

---

75. King, *supra* note 70, at 333 (internal citations omitted). Federal regulations speak of "direct benefits" but do not define them. See, e.g., 45 C.F.R. § 46.405 ("HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of *direct benefit* for the individual subject . . . only if the [certain criteria are met]." (emphasis added)). They do, however, generally instruct IRBs to evaluate only the risks and benefits of the research rather than evaluating the risks and benefits of therapies provided to subjects not involved in the research. 45 C.F.R. § 46.111(a)(2). Because the children in the Kennedy Krieger study received a heightened level of monitoring that might provide timely and worthwhile diagnostic information beyond routine healthcare, perhaps some IRBs would characterize these benefits as direct although they were not the result of the research but merely incident to being in the study. Unfortunately, the federal regulations provide little guidance to aid in making such a conclusion.

76. See generally King, *supra* note 70, at 333 (describing the types of possible benefits to be received for research participation).

77. See generally 45 C.F.R. §§ 46.401-409 (discussing the supplementary requirements for research involving child subjects).

78. A current debate exists concerning whether it is ethical to combine "risk-minimization features and collateral benefit features into one package, and [to then] view the whole study as providing direct benefit." King, *supra* note 70, at 339. Kopelman notes that Kennedy Krieger might have characterized the screening and education benefits as direct under a "medical or public health model" because the children were "at risk" and therefore appropriate subjects for a study with greater than minimal risk. Kopelman, *supra* note 62, at 44. However, Kopelman questions this characterization "if the court in *Grimes* is correct on the facts and the investigators had some role in placing or keeping some children in homes with lead hazards." *Id.* at 44.

79. Direct and collateral benefits may become conflated by research designs. King, *supra* note 70, at 339.

80. See generally *id.* Ross argues that all homes other than the control groups received some lead abatement, and thus, subjects were benefited. Ross, *In Defense*, *supra* note 62, at 50-51. This argument ignores the evidence suggesting that some homes were vacant, and therefore, the children recruited to those homes may not have benefited from moving into those particular homes rather

homes that later underwent repair and maintenance for the research received some direct benefit because the lead levels in their homes were presumably reduced. It remains unclear whether the children who moved into the remediated homes upon entering the study directly benefited because there is no way to determine the level of lead, if any, that was present in alternative housing. Thus, these children could have either benefited or have been put at increased risk. Children in control groups four through five received no direct benefit since repair and maintenance was not undertaken in their homes. All children received benefits by virtue of blood test monitoring and the information their families received regarding lead contamination in their homes. These benefits, however, were not the result of the tested intervention, but rather, they merely constitute indirect benefits resulting from inclusion in the study. Identification of direct and indirect benefits baffles IRBs. As the National Bioethics Advisory Commission (NBAC) explained, the analysis is quite murky:

[I]RBs should be cautious in classifying procedures as offering the prospect of direct benefit. In fact, if it is not clear that a procedure also offers the prospect of direct benefit, IRBs should treat the procedure as one solely designed to answer the research question(s). A major advantage of this approach is that it avoids justifying the risks of procedures that are designed solely to answer the research questions based on the likelihood that another procedure in the protocol is likely to provide a benefit.<sup>81</sup>

In addition to their failure to provide a careful benefit analysis, the IRB neglected to appreciate the risks presented by the study. For example, the consent form did not fully acknowledge the risks.<sup>82</sup> Yet, the study either knowingly allowed children to be exposed to a continuing danger<sup>83</sup> or actually increased exposure risks for others by placing some subjects in homes where lead abatement was unfinished.<sup>84</sup> The fact that

---

than non-study homes.

81. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 13.

82. *Grimes*, 782 A.2d at 844.

83. Yet, Kennedy Krieger maintained that when lead blood levels rose, it recommended appropriate medical intervention be sought. *Lead-Based Paint Study*, *supra* note 36.

84. In *Ericka Grimes's* case, her family resided in a home on Monroe Street in Baltimore from 1990 to 1994. *Grimes*, 782 A.2d at 824. The Monroe property was arguably assigned to Group IV (although this issue was not fully resolved) since the property had been previously remediated. *Id.* at 824 n.21. Ericka was born in 1992, and she was recruited to the study in 1993. *Id.* at 824. "Hot spots," higher levels of lead dust, were discovered in March 1993 but not revealed to the family until December 1993. *Id.* at 825. Although blood tests on Ericka in April 1993 were within the normal range, two subsequent blood tests showed increasing blood lead levels. *Id.* One blood test rose to the highly elevated range. *Grimes*, 782 A.2d at 825 n.23. The plaintiffs alleged that the defendants breached a duty to inform them of the hot spots and allowed Ericka to contract lead poisoning. *Id.* at 826. Plaintiff Myron Higgins moved with her family into a Level II remediated home in 1994 shortly after incomplete remediation. *Id.* at 826-27. The child's blood lead levels

when the IRB first rejected the study it referred to healthy control children as problematic,<sup>85</sup> evidences that the IRB was likely concerned about exposing the control children to the risks and discomforts of the periodic blood drawing without first identifying the proportionate benefits. Perhaps in order to justify those risks to the control population, the IRB clarified that education on lead poisoning and information provided to parents regarding their children's test results benefited the entire study group.<sup>86</sup>

The IRB, however, apparently did not appreciate the risks the subjects in the experimental group may have been exposed to or the uncertainty of the benefits of abatement. Kennedy Krieger asserted in litigation and press releases that the IRB regarded the lead abatement activities in groups one, two, and three as beneficial to children.<sup>87</sup> The IRB's assumption proves problematic, however, because a number of the children were placed into the homes that were only partially remediated.<sup>88</sup> In fact, the research question was how much remediation needs to be undertaken to protect children from lead poisoning. Therefore, these children may have been exposed to risks, and hence, placed in a worse position rather than a healthier, beneficial one. The researchers should have identified the risk of lead exposure in all of the homes involved in the study as a risk of participation. The participants who moved into these homes now lived in residences that were previously contaminated and were currently being used to determine the level of repair and maintenance needed in order to effectively minimize lead exposure. Moreover, even for children already residing in lead contaminated homes, the study created an increased risk. If the remediation undertaken in this study was inadequate, then assuming the researchers effectively decreased the lead levels in these homes, they still perpetuated a risk to children in homes with some level of lead. Finally, as the plaintiffs alleged, by participating in the study, the families were lulled into complacency.<sup>89</sup> For example,

---

fluctuated. The highest blood lead level placed the child in Class III, and her mother was advised to "provide the test result to [her] child's primary health care provider right away." *Id.* at 828 (internal quotation marks omitted). Plaintiffs contended that the researchers recorded high levels of lead contaminated dust but failed to disclose this fact. *Id.* at 829. Instead, relying on a second testing method (dust wipe samples), the researchers led Myron's mother to believe that the house was clean. *Grimes*, 782 A.2d at 829. Plaintiffs alleged that only informing the mother of the "lower results of the samples collected by dust wipe methodology was misleading" and "gave her a false sense of security that there were no potential lead-based paint or dust hazards in her house." *Id.*

85. *See id.* at 814.

86. *See id.* at 813-14, 847-48.

87. *See, e.g., Lead-Based Paint Study*, *supra* note 36 ("[K]KI believed this Study would provide benefits to the Study participants since all participants would be living in housing that had been improved or was new and would be monitored for blood lead levels on an ongoing basis.").

88. Kennedy Krieger denied that families were lured into homes that were not fully abated. *Id.*

89. *See, e.g., Grimes*, 782 A.2d at 826 ("[Appellant] and her mother continued to reside in the home unaware of the hazards and unaware of the dangers to which [appellant] was being ex-

the plaintiff participants complained that all of the attendant blood and home inspections wrongfully caused them to believe that their children as well as their homes were safe and regularly monitored for lead.<sup>90</sup>

Regulations governing risk and benefit assessment in child studies are complex and difficult to navigate.<sup>91</sup> The concept, however, is relatively simple: "As the risk of harm to the child increases, greater restrictions are imposed."<sup>92</sup> Where research involves no more than minimal risks to the child,<sup>93</sup> the research is permissible if one parent consents and the child assents.<sup>94</sup> If the research exposes a child to greater than minimal risk but also holds potential for direct benefit, in addition to these aforementioned requirements,<sup>95</sup> the IRB must also determine that "[t]he risk is justified by the anticipated benefit to the subjects" and that "[t]he relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches."<sup>96</sup> In contrast, research that offers the potential for direct benefit to the child and involves greater than minimal risk is permissible with assent and permission of both parents,<sup>97</sup> and when the following requirements are met:

The risk represents a minor increase over minimal risk; [t]he intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; [t]he intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and [a]dequate provisions are made for soliciting assent of the children and permis-

---

posed.").

90. *Id.* at 825-26, 828. Families were given blood test results promptly, but results of home testing for lead contamination were delayed. *Id.* at 826. Moreover, the results of Cyclone testing were never provided although Kennedy Krieger claimed this withholding was justifiable because the Cyclone vacuum was merely experimental. *Id.* at 845.

91. See generally Jennifer Rosato, *The Ethics of Clinical Trials: A Child's View*, 28 J.L. MED. & ETHICS 362, 366 (2000) ("The complex provisions of HHS Subpart D [the federal regulations dealing with additional protections for child subjects] are guided by a matrix of factors . . .").

92. *Id.*

93. Minimal risk is the only risk defined by federal regulation, and it means "that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." 45 C.F.R. § 46.102(i).

94. Rosato, *supra* note 91, at 366; see also 45 C.F.R. § 46.408(a) (describing the requirement of assent by children). When dealing with children too young to provide mature assent, IRBs must make an additional judgment "that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research." *Id.*

95. 45 C.F.R. § 46.408 (b).

96. 45 C.F.R. § 46.405 (a)-(b).

97. 45 C.F.R. § 46.408 (b).

sion of their parents or guardians.<sup>98</sup>

The Kennedy Krieger research presented several issues concerning risk. The quarterly blood draws on healthy children did not likely constitute a greater than minimal risk. Although uncomfortable to a healthy child and somewhat more excessive than typical to a normal child's health experiences, these blood withdrawals were not uncharacteristically outside the scope of their experiences.<sup>99</sup> In addition, the questionnaires and family home studies should also likely be characterized as no greater than minimal risk because aside from time and perhaps some invasion of privacy, the children were not realistically harmed as a result. The core of the research, however, presented risks that were apparently underestimated by either the researchers or the IRB. First, while researchers noted that many homes in Baltimore were contaminated with lead and not abated, some of these units were either not in the rental market or not rented to vulnerable children. The study protocol, however, brought several of these homes into the rental market or facilitated their rental to the participant parents.<sup>100</sup> Second, all homes included in the study were required to either have undergone abatement to some prescribed degree, or if in a control group, to have been previously abated or of modern (and therefore, lead-free) origin.<sup>101</sup> The heart of the study, however, centered on the recognition that the level of abatement necessary to reduce the risk of lead poisoning in previously contaminated homes was unknown.<sup>102</sup> Thus, by its design, the study proposed to attract families with children or induce families with children to remain in homes that may or may not have been adequately lead-abated.<sup>103</sup>

The consent form explained to parents that the study proposed to de-

---

98. 45 C.F.R. § 46.406 (a)-(d). The Kennedy Krieger children were not necessarily lead toxic at the outset of the study, and thus, for purposes of this regulation, they did not have a disorder or condition that might be improved by their participation in the study.

99. See IRB GUIDEBOOK, *supra* note 59, at ch. 6 pt. C ("Procedures that usually present no more than minimal risk to a healthy child include: urinalyses, obtaining small blood samples, EEGs, allergy scratch tests, minor changes in diet or daily routine, and/or the use of standard psychological or educational tests.").

100. *Grimes*, 782 A.2d at 826. For example, the home into which Myron Higgins moved was vacant until the property owner accepted it into Group II when it was, thereafter, partially abated. *Id.* The landlord then rented the property to the Higgins family. *Id.* at 827.

101. *Id.* at 822-23.

102. *Id.* at 819.

103. It is unclear from the available information whether Kennedy Krieger viewed the three levels of abatement as in "equipoise." "Equipoise" exists where there is genuine uncertainty as to what treatment is preferable. Benjamin Freedman, *Equipoise and the Ethics of Clinical Research*, 317 N. ENG. J. MED. 141, 141 (1987) (internal citations omitted). Whether the researchers were genuinely uncertain as to the effect of the three levels is unclear. Their information sheet suggests that all three levels of abatement reduced lead in homes by eighty percent. However, the purpose of the study was to test the effectiveness of the various levels of remediation on exposure. *Lead-Based Paint Study*, *supra* note 36. Yet, a logical inference is that the group receiving the most remediation enjoyed more lead abatement in their homes.

termine how well "two levels of repair work" succeeded in reducing exposure to lead paint.<sup>104</sup> Moreover, it warned parents that "lead poisoning in children is a problem in Baltimore City,"<sup>105</sup> and that they were selected to participate in the study so to have repair work done on their homes in order to decrease exposure to lead paint and dust.<sup>106</sup> The form further informed parents that "[t]he repairs [were] not intended, or expected, to completely remove exposure to lead."<sup>107</sup> Despite these general acknowledgements, the consent form failed to explain that the remaining lead contamination in the home could result in lead exposure and toxicity.<sup>108</sup> Most remarkably, it failed to identify any risks associated with the study and, in fact, did not even contain a risk section.<sup>109</sup>

### B. Landmark Decision

1. *The Legal Bases for the Researcher's Duties.*—In *Grimes*, the court reversed the trial court's grant of summary judgment in favor of Kennedy Krieger.<sup>110</sup> Holding that three distinct legal theories could create a special relationship between researcher and human subjects for the purpose of negligence liability,<sup>111</sup> the court explained that these relationships must be determined on a "case-by-case basis."<sup>112</sup> The court explained that a special relationship between the researchers and the human subjects in this instance may arise from federal regulations protecting human subjects, the Nuremberg Code, contractual obligations based on the design of the research and parental consent, and by the special relationship created between the researcher and the subject, particularly in light of a child's vulnerability.<sup>113</sup>

---

104. *Grimes*, 782 A.2d at 824.

105. *Id.*

106. *Id.*

107. *Id.* This statement is particularly ambiguous, however, and raises questions: Did the remaining exposure that the form refers to mean lead in the home or lead exposure outside the home? Did the use of the words "intended, or expected" mean that the researchers intended to leave some lead contamination behind after remediation?

108. *Id.* at 844.

109. *Grimes*, 782 A.2d at 844. Federal regulations require consent documents to inform the subjects of potential risks or discomforts. 45 C.F.R. § 46.116(a)(2).

110. *Grimes*, 782 A.2d at 858.

111. *Id.* Remarkably, Kennedy Krieger later retreated from its assertion that it owed no legal duty to plaintiffs:

While in the lower court, KKI's insurance lawyers made a legalistic argument that KKI had "no legal duty" to report the dust levels to families. KKI regrets this technical argument and wants to reassure the public that in this Study, and in all past and future studies, KKI has been and is committed to families and all persons in its research trials.

*Lead-Based Paint Study*, *supra* note 36.

112. *Grimes*, 782 A.2d at 858 ("We hold that there was ample evidence in the cases at bar to support a fact finder's determination of the existence of duties arising out of contract, or out of a special relationship, or out of regulations and codes, or out of all of them, in each of the cases.").

113. *Id.*



The court pointed to the contractual characteristics in the relationship between researchers and their subjects.<sup>114</sup> Researchers promised to provide each family with compensation, information on the lead levels in their child's blood, and information regarding lead poisoning.<sup>115</sup> In return, parents consented on behalf of themselves and their children to make their children available for blood tests, answer questionnaires periodically, and to grant researchers access to their homes in order to test for lead.<sup>116</sup> The court held that based on the record, "mutual assent, offer, acceptance, and consideration existed, all of which created contractual relationships imposing duties by reason of the consent agreement."<sup>117</sup> Accordingly, this relationship constituted a "bilateral contract between the parties," which required "full, detailed, prompt, and continuing warnings as to all the potential risks and hazards inherent in the research or that arise during the research."<sup>118</sup> Thus, study participation created a contractual relationship between researchers and their subjects.<sup>119</sup>

The court further determined that the lower court erred in holding that a special relationship cannot arise from the duties a researcher owes to a research subject.<sup>120</sup> Instead, the appellate court reasoned that only in rare instances, such as research involving studies of "compilation of already extant statistics," a researcher-subject relationship might not impose researcher duties to subjects.<sup>121</sup> As a general rule, however, "the creation of study conditions or protocols or participation in the recruitment of otherwise healthy subjects to interact with already existing, or potentially existing, hazardous conditions, or both, for the purpose of creating statistics from which scientific hypotheses can be supported," typically establishes "special relationships as a matter of law."<sup>122</sup>

Thus, the court held that exposing healthy subjects, particularly children whose parents must consent for them, to the risks associated with this study, warranted the imposition of a special relationship with its concomitant duties in tort.<sup>123</sup> In its defense, Kennedy Krieger asserted that it was nothing more than an "institutional volunteer" and that it owed no duty to protect the subjects.<sup>124</sup> Taking into account the grant

---

114. *Id.* at 819.

115. *Id.* at 843.

116. *Id.* Research subjects retain an absolute and unfettered right to withdraw from research at any time. 45 C.F.R. § 46.116(a)(8) (stating that the informed consent must provide a statement informing subject that he/she "may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled").

117. *Grimes*, 782 A.2d at 843.

118. *Id.*

119. *Id.* at 844.

120. *Id.* at 858.

121. *Id.* at 845-46.

122. *Grimes*, 782 A.2d at 846.

123. *Id.*

124. *Id.*

money it received to conduct the research, the court questioned Kennedy Krieger's volunteer status,<sup>125</sup> and it then refused to afford immunity status to researchers involved in human subject experimentation absent a legislative directive to do so.<sup>126</sup>

The court also evaluated the special duties arising from the duties imposed by federal regulations and the Nuremberg Code. Beginning by noting that "[a] duty may be prescribed by a statute, or a special relationship creating duties may arise from the requirement for compliance with statutory provisions,"<sup>127</sup> the court examined the panoply of federal regulations designed to ensure that federally funded or sponsored research is "conducted in accordance with sound ethical principles."<sup>128</sup> The court focused on the special federal provisions designed to give added protection to children,<sup>129</sup> as well as regulations ensuring fully informed consent.<sup>130</sup> According to the court, a special relationship establishing duties may arise from federally imposed regulations.<sup>131</sup> Because these duties continue throughout the course of the research, researchers are required to inform participants when risks are presented or altered.<sup>132</sup> Thus, the court allowed a cause of action by human subjects based upon a researcher's violations of federal regulations intended for human subject protection.

Remarkably, the court also looked to the Nuremberg Code as one source describing a researcher's duty to her human subjects.<sup>133</sup> This judi-

---

125. *Id.* at 846 n.36.

126. *Id.* at 846.

127. *Grimes*, 782 A.2d at 846.

128. *Id.* at 848 (quoting 45 C.F.R. § 46.407(b)(2)(ii)).

129. *Id.* at 846, 848; *see also* Additional Protections for Children Involved as Subjects in Research, 45 C.F.R. §§ 46.401-409.

130. *Grimes*, 782 A.2d at 846-49.

131. *Id.* at 849.

132. *Id.*

133. *Id.* The Nuremberg Code states:

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experi-

cial adoption of the Nuremberg Code as a source of ethics in research provides courts with a comprehensive structure, independent of federal statutory law, by which to judge research ethics. Although the court recognized that the Code was intended for international application,<sup>134</sup> it nevertheless held that "[t]he breach of obligations imposed . . . by the Nuremberg Code, might well support actions sounding in negligence in such cases as those at issue here."<sup>135</sup> By determining that in tort law, the researcher-subject relationship is distinctive, and by adopting the Nuremberg Code as a methodology for judicial review of human research, the court carved out a powerful position for the judiciary, separate from the federal regulatory system, to act in protecting human research subjects. The moral force of the Nuremberg Code's two fundamental concepts of voluntary consent and risk-benefit analysis is unassailable.<sup>136</sup>

---

mentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seemed to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably [sic] cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

IRB GUIDEBOOK, *supra* note 59, at app. 6. A historical account of the Nazi doctor trials, the development of the Nuremberg Code, and its ethical underpinnings is provided in *THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION* (George Annas & Michael A. Grodin eds., 1992).

134. *Grimes*, 782 A.2d at 849. See generally Dawn Joyce Miller, Comment, *Research Accountability: The Need for Uniform Regulation of International Pharmaceutical Drug Testing*, 13 PACE INT'L L. REV. 197, 202-05 (2001) (noting the influence of the Code in general but recognizing its limited role as binding authority in international law).

135. *Grimes*, 782 A.2d at 849. The court explained that the Code, while never judicially adopted, provided the "most complete and authoritative statement of the law of informed consent to human experimentation," and it "may be applied, in both civil and criminal cases, by state, federal, and municipal courts in the United States." *Id.* at 835 (quoting George J. Annas, *Mengele's Birthmark: The Nuremberg Code in United States Courts*, 7 J. CONTEMP. HEALTH L. & POL'Y 17, 21 (Spring 1991)).

136. As others have noted, the Nuremberg Code has been cited from time to time, but "no U.S. court has ever awarded damages to an injured experimental subject, or punished an experimenter, on a basis of a violation of the Code." Jeffrey H. Barker, *Human Experimentation and the Double Facelessness of a Merciless Epoch*, 25 N.Y.U. REV. L. & SOC. CHANGE 603, 608 (1999) (quoting George J. Annas, *The Nuremberg Code in U.S. Courts: Ethics Versus Expediency*, in *THE NAZI DOCTORS*, *supra* note 133, at 201).

These precepts are the foundation of the current federal schema and to the extent the court drew from them general principles of ethics and customary practices it is not surprising. However, particular provisions within the Code could heighten researchers' responsibilities and limit research activities beyond current law, putting it at odds with federal regulations.<sup>137</sup> For example, the Code's stringent requirement that all subjects have legal capacity and give voluntary consent and its lack of any specific guidance concerning children and the incapacitated could curtail research on these populations generally.<sup>138</sup>

2. *KKI Likely Breached Its Duties.*—The court identified three instances in which Kennedy Krieger may have breached its duty to the participants involved in the study. First, the court noted that the parents were not likely provided with adequate information about the nature of the study and the risks to the children.<sup>139</sup> According to the court, the consent form was flawed because it failed to "directly inform the parents . . . it was contemplated that some of the children might ingest lead dust particles,"<sup>140</sup> and the children's blood was tested in order "to evaluate how effective the various abatement measures" proved.<sup>141</sup> The court further noted that "a reasonable parent would expect to be clearly informed" that lead ingestion was anticipated.<sup>142</sup> As the court explained, Kennedy Krieger should have informed the parents that the researchers intended for the children to remain in the "house until the conclusion of the study,"<sup>143</sup> which may conceivably lead to "some accumulation of lead in the [children's] blood."<sup>144</sup> Finally, the court explained that although this information may have effectively dissuaded parents from enrolling in the study, that fact alone did not constitute a ground to exclude it from the consent form.<sup>145</sup>

Second, in reversing summary judgment, the court held that regardless of the completeness of the disclosure and the presence of parental consent, the research design may have been fundamentally flawed, and

---

137. See Kendall Ann Desaulniers, *Legislation to Protect the Decisionally Incapacitated Individual's Participation in Medical Research: Safety Net or Trap Door?*, 13 REGENT U.L. REV. 179, 183 (2000) (commenting that the Declaration of Helsinki was promulgated, in part, to address restrictive provisions of the Nuremberg Code).

138. See Ann E. Ryan, Comment, *Protecting the Rights of Pediatric Research Subjects in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*, 23 FORDHAM INT'L L.J. 848, 866-68 (2000) (noting critics who consider "the Code as too restrictive to allow for human experimentation using any subjects other than competent adults").

139. *Grimes*, 782 A.2d at 844.

140. *Id.*

141. *Id.*

142. *Id.*

143. *Id.*

144. *Grimes*, 782 A.2d at 844.

145. *Id.*

as a result, it might have exposed children to an impermissible risk.<sup>146</sup> In a sweeping statement, the court opined, “otherwise healthy children should not be the subjects of non-therapeutic experimentation or research that has the potential to be harmful to the child.”<sup>147</sup> Accordingly, neither the subject’s consent nor IRB approval eliminates the researcher’s duty.<sup>148</sup> Rather, the researcher must fulfill the duty of obtaining consent, but the researcher’s “duty to a vulnerable research subject is independent of [that] consent.”<sup>149</sup> As the court explained, research, by its very nature and objective, may subordinate the subject’s health “to the dictates of a research protocol designed to advance knowledge for the sake of future patients.”<sup>150</sup> Although this objective is clearly important, research requires fundamental safeguards that were likely absent in the Kennedy Krieger study.<sup>151</sup> In light of the attendant risks to vulnerable subjects, the court concluded, at least for summary judgment purposes, “no degree of parental consent, and no degree of furnished information to the parents could make the experiment at issue here, ethically or legally permissible. It was wrong in the first instance.”<sup>152</sup>

Third, the court severely circumscribed the parameters of parental consent in non-therapeutic research. The court explained that henceforth, in Maryland, “a parent . . . cannot consent to the participation of a child or other person under legal disability in non-therapeutic research or studies in which there is any risk of injury or damage to the [child’s] health.”<sup>153</sup> Therefore, even if full disclosure occurred, the nature of the risks were such that parents should not have been permitted to consent to these risks.<sup>154</sup> This parental limitation is based on the broader social obligation to protect children generally. As the court explained, “it is unacceptable to expose otherwise healthy children, incapable of personal assent (consent), to a non-therapeutic research environment that is known at the inception of the research, might cause the children to ingest lead dust.”<sup>155</sup> This study was particularly troubling since one “measurement of the [experiment’s] success . . . [was] determined by the extent to which the blood of the children absorbs, and is contaminated by, a substance that the researcher knows can . . . cause serious and long term adverse

---

146. *Id.* at 850-51.

147. *Id.* at 850.

148. *Id.*

149. *Grimes*, 782 A.2d at 850.

150. *Id.* at 851 (quoting Jay Katz, *Human Experimentation and Human Rights*, 38 ST. LOUIS U. L.J. 7, 8 (1993)).

151. *Id.* at 852.

152. *Id.* at 857-58.

153. *Id.* at 858. This holding alarmed amici organizations. They asserted in a motion for reconsideration that the court’s ruling would adversely curtail pediatric research and undermine their customary practices. Kopelman, *supra* note 62, at 41.

154. *Grimes*, 782 A.2d at 852-58.

155. *Id.* at 853.

health effects.”<sup>156</sup> The court later clarified that “any risk” means “any articulable risk beyond the minimal kind of risk that is inherent in any endeavor.”<sup>157</sup>

By imposing a duty on researchers to obtain judicial review prior to enrolling children in non-therapeutic research that poses risks, the *Grimes* decision has far reaching implications. In the Kennedy Krieger research, neither the researchers nor the parents sought impartial judicial review prior to commencement of the study.<sup>158</sup> According to the court, in the absence of a mandate requiring judicial review, researchers and scientific review boards would constitute “the sole judges of whether it is appropriate to use children in nontherapeutic research.”<sup>159</sup> As the court recognized, it would be a serious mistake to allow science alone to determine “the appropriateness of such research methods on human subjects, especially in respect to children.”<sup>160</sup> By requiring judicial review, children will be better protected from research abuses. The courts’ role in this process would be to establish the child’s interest as paramount to all others. According to the court, courts will refuse to “defer to science.”<sup>161</sup> Therefore, the court established itself as the ultimate guardian of the child’s best interests. As the court explained, regardless of the interests of parents and “of the general public in fostering research that might, according to a researcher’s hypothesis, be for the good of all children, this Court’s concern for the particular child and particular case, over-arches all other interests.”<sup>162</sup> The court then stated that “[i]t is simply . . . not in the best interest of any healthy child to be intentionally put in a non-therapeutic situation where his or her health may be impaired, in order to test methods that may ultimately benefit all children.”<sup>163</sup> Thus,

---

156. *Id.*

157. *Id.* at 862.

158. *Id.* at 855.

159. *Grimes*, 782 A.2d at 855.

160. *Id.* The court relied on *Hart v. Brown*, 289 A.2d 386 (Conn. Super. 1972), which involved a kidney donation and transplant between seven-year-old identical twins, and *Strunk v. Strunk*, 445 S.W.2d 145 (Ky. 1969), involving sibling organ donation by a mentally incompetent donor.

What is of primary importance to be gleaned in the *Hart* and *Strunk* cases is not that the parents or guardians consented to the procedures, but that they first sought permission of the courts, and received that permission, before consenting to a non-therapeutic procedure in respect to some of their minor children, but that was therapeutic to other of their children.

*Grimes*, 782 A.2d at 854-55.

161. *Id.* at 855.

162. *Id.* at 853.

163. *Id.* The court’s holding is in accord with the notion that a parent should not be able to foreclose a child’s right to an open future without judicial review. *Id.* at 812-17, 824-25. Thus, parents and physicians should not be able to make unilateral decisions on sterilization and other life-altering elective surgery for children without judicial review. See Hazel Glenn Beh & Milton Diamond, *An Emerging Ethical and Medical Dilemma: Should Physicians Perform Sex Assignment Surgery on Infants with Ambiguous Genitalia?*, 7 MICH. J. GENDER & L. 1, 37-45, 57-58 (2000) (questioning parental and physician decision-making authority to consent to or perform sex assignment surgery on infants with ambiguous genitalia without judicial review).

the court concluded that the current ethical obligations placed on researchers to ensure protection of human subjects, the IRB's independent review of the project, and parental consent are not sufficient safeguards to protect children subjects.<sup>164</sup> By acknowledging the flaws in the current system, this holding established a prospective judicial role in protecting child subjects well beyond post-injury compensation. In light of an increasing recognition that the federal system is inadequate to protect human subjects, the *Grimes* decision suggests an expanded judicial role in the protection of human subjects.

### III. THE IRB AS THE FRONT LINE IN THE PROTECTION OF HUMAN SUBJECTS

The *Grimes* court was not alone in concluding that the current system is seriously deficient.<sup>165</sup> For the past twenty-five years, institutions conducting human subject research with Health and Human Services sponsorship or funding have been required to abide by a complex body of federal regulations designed to protect human subjects.<sup>166</sup> Largely in response to the Tuskegee Syphilis Study,<sup>167</sup> the National Research Act enacted in 1974 established regulations designed to protect human research subjects.<sup>168</sup> Under these new regulations, "the IRBs—rather than principal investigators—became responsible for determining whether potential research subjects are 'at risk,' and if so, whether the risks outweigh pos-

---

164. *Grimes*, 782 A.2d at 814-18. Arising out of similar concerns for children as a vulnerable class, others have also considered the limits of parental authority to consent on behalf of children. Compare Lainie Friedman Ross, *Children as Research Subjects: A Proposal to Revise the Current Federal Regulations Using a Moral Framework*, 8 STAN. L. & POL'Y REV. 159, 166-69 (1997) (arguing that research on children that poses more than a minor increase over minimal risk without "proportionate benefit" to the child "is immoral," but also stating that parents should be able to consent to non-therapeutic minimal risk research).

165. In 1998, the Office of Inspector General issued an extensive report warning that IRBs are not equipped to adequately fulfill the review and approval requirements expected of them. Department of Health and Human Services, Office of Inspector General, OEI-01-97-00193, *Institutional Review Boards: A Time for Reform* iii (June 1998) <http://oig.hhs.gov/oei/reports/a276.pdf> [hereinafter Inspector General, *Time for Reform*]. Numerous researchers have also explained that the current IRB system does not adequately protect human subjects and should be overhauled. See, e.g., James F. Childress, *The National Bioethics Advisory Commission: Bridging the Gap in Human Subjects Research Protections*, 1 J. HEALTH CARE L. & POL'Y 105, 113-14 (1998); Jay Katz, *Human Experimentation and Human Rights*, 38 ST. LOUIS U. L.J. 7, 9 (1993); Adil E. Shamoo, *Institutional Review Boards (IRBs) and Conflict of Interest*, 7 ACCOUNTABILITY IN RESEARCH 201, 205-07 (1999) [hereinafter Shamoo, *Conflict of Interest*]; Alison Wichman, *Protecting Vulnerable Research Subjects: Practical Realities of Institutional Review Board Review and Approval*, 1 J. HEALTH CARE L. & POL'Y 88, 97-102 (1998).

166. See 45 C.F.R. §§ 46.101-409 (2002); 21 C.F.R. §§ 56.101-124 (2002).

167. Anderlik & Elster, *supra* note 1, at 222. In the Tuskegee Syphilis Study, "approximately 400 African-American men with syphilis were left untreated to try to gain a scientific understanding of the progression of the disease. Although the study had been ongoing since the 1930s, it was not until a 1972 newspaper story about the research that the public became aware of the deficiencies of the study." *Id.*

168. *Id.*

sible benefits to them and the importance of the knowledge to be gained from the research.”<sup>169</sup> In addition, the Act also “led to the establishment of the OPRR<sup>170</sup> and the National Commission for the Protection of Human Subjects,”<sup>171</sup> which was responsible for examining the problems in research involving human subjects and recommending guidelines.<sup>172</sup> Furthermore, the FDA issued regulations, and “[i]n 1981, the Department of Health and Human Services (DHHS) revised the regulations . . . found at 45 C.F.R. § 46 and, in 1983, added Subpart D to provide additional protections for children participating in research,”<sup>173</sup> which were subsequently adopted by “fifteen other federal agencies and became known as the Common Rule.”<sup>174</sup> In addition to the Common Rule, typically, under assurances negotiated with the federal government, institutions also “pledg[e] conformity with the regulations [for] all research, irrespective of the source of funding.”<sup>175</sup> In order to adequately protect human subjects, the system anticipates that there will be a check on the researcher and that researchers will design experiments that protect participants.<sup>176</sup>

---

169. *Id.* (quoting James Bell et al., *Final Report: Evaluation of NIH Implementation of Section 491 of the Public Health Service Act, Mandating a Program of Protection for Research Subjects* 12 (1998), available at [http://ohrp.osophs.dhhs.gov/hsp\\_report/hsp\\_final\\_rpt.pdf](http://ohrp.osophs.dhhs.gov/hsp_report/hsp_final_rpt.pdf)).

170. The Office for Protection from Research Risks (OPRR) was established in 1972 to ensure the protection of human subjects participating in U.S. Department of Health and Human Services-sponsored research. In 2000, the office was succeeded by the Office of Human Research Protections (OHRP) with the intent to “elevate its stature and effectiveness.” HHS Fact Sheet, Department of Health and Human Services (June 6, 2000), available at <http://www.hhs.gov/news/press/2000pres/20000606a.html>.

171. Anderlik & Elster, *supra* note 1, at 222-23.

172. *Id.* at 223.

173. *Id.*

174. *Id.* The Common Rule is the federal policy extending the protections of human subjects requirements to the United States Department of Agriculture, Department of Energy, National Aeronautics and Space Administration, Department of Commerce, Consumer Product Safety Commission, International Development Cooperation Agency, Agency for International Development, Department of Housing and Urban Development, Department of Justice, Department of Defense, Department of Education, Department of Veterans Affairs, Environmental Protection Agency, National Science Foundation, Department of Health and Human Services, and Department of Transportation. See Federal Policy for the Protection of Human Subjects, 56 Fed. Reg. 28,003 (1991). The Common Rule unified regulatory language “did not create a shared mechanism for interpreting and implementing the regulations,” and thus, there is little uniformity. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 9. Some federal agencies have supplanted the Common Rule with additional provisions, compounding IRB confusions over regulations. *Id.* at 11. And because each agency is a signatory, the Rule is difficult to amend, resulting in agency deviations by regulatory guidance. *Id.*

175. Jesse A. Goldner, *An Overview of Legal Controls on Human Experimentation and the Regulatory Implications of Taking Professor Katz Seriously*, 38 ST. LOUIS U. L.J. 63, 99 (1993).

176. *Id.* at 98 (citing The National Commission for the Protection of Human Subjects of Biomedical and Behavior Research, Department of Health, Education, and Welfare, Pub. No. (OS) 78-0008, *Institutional Review Boards: Report and Recommendations* (1978) (stating that the IRB system serves as an independent check on the researcher’s self interest). As one commentator explained:

IRBs are important because research investigators have an inherent conflict of interest. As health care professionals, they are dedicated to promoting the welfare of individual patients; as researchers, they seek generalizable knowledge applicable to persons other than their individual patients. Because the second goal may come in



The lynchpin of the federal system<sup>177</sup> is the requirement that under a written assurance the institution supplies to the government, it promises to establish and maintain an Institutional Review Board to independently review and approve research.<sup>178</sup> The regulatory provisions attempt to ensure adequate review by mandating that IRB members have sufficient experience, competence, and independence to perform their tasks.<sup>179</sup> Each IRB must consist of at least five members "with varying backgrounds."<sup>180</sup> At least one member must be unaffiliated with the institution.<sup>181</sup> In addition, one member must principally represent scientific concerns, whereas one must represent nonscientific concerns.<sup>182</sup> Members who have conflicts of interest are prohibited from participating in decision-making.<sup>183</sup>

The underpinnings of the technical substantive and procedural rules that guide the conduct and deliberations of IRBs were taken from the Nuremberg Code,<sup>184</sup> the World Medical Association Declaration of Helsinki,<sup>185</sup> and particularly the Belmont Report,<sup>186</sup> three profoundly simple

conflict with the first, our society has decided that an objective review of human subjects research by a group of diverse individuals is most likely to protect human subjects and promote ethically sound research.

Wichman, *supra* note 165, at 92.

177. The federal government funds a substantial amount of medical research. Darren E. Zinner, *Medical R & D at the Turn of the Millennium*, HEALTH AFFAIRS, Sept. 1, 2001, available at 2001 WL 10696976. "Federal obligations for life science and medical research increased . . . from \$1.01 billion in 1967 . . . to \$16.17 billion in 1999." *Id.*

178. 45 C.F.R. § 46.103(b).

179. 45 C.F.R. § 46.107(a). Section 46.103 requires that the IRB expertise be adequate in light of the scope of the research conducted at the institution. 45 C.F.R. § 46.103(d). This is interpreted to include knowledge of the local research community, so that where research is conducted outside the geographical confines of the institution, the IRB must carefully document how it has ensured that it was adequately informed of that local community, through the expertise of its membership, through expert consultation, through visitation or by other methods. See Department of Health and Human Services, Office of Human Research Participants, *IRB Knowledge of Local Research Context*, available at <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/local.htm>. The federal government's demand for documentation of this is clear. See, e.g., Compliance Letter to Chi Van Dang, The Johns Hopkins University, Human Research Subject Protections Under Multiple Project Assurance M-1011, (Oct. 3, 2001), available at [http://ohrp.osophs.dhhs.gov/detrm\\_letters/oct01a.pdf](http://ohrp.osophs.dhhs.gov/detrm_letters/oct01a.pdf) ("At its July 31, 2001 meeting, the IRB approved a clinical trial that was to be conducted in Brazil. It is unclear which members of the IRB had expertise regarding the local context where this research was to be conducted. Please respond.").

180. 45 C.F.R. § 46.107(a).

181. 45 C.F.R. § 46.107(d).

182. 45 C.F.R. § 46.107(c).

183. 45 C.F.R. § 46.107(e).

184. See Leonard H. Glantz, *The Influence of the Nuremberg Code on U.S. Statutes and Regulations*, in THE NAZI DOCTORS, *supra* note 133, at 183-200. The Nuremberg Code, espousing voluntary consent and respect for individuals as the cornerstone of experimentation, was developed by the International Military Tribunal that tried Nazi physicians for the medical experimentation conducted on concentration camp inmates without consent. See Michael A. Grodin, *Historical Origins of the Nuremberg Code*, in THE NAZI DOCTORS, *supra* note 133, at 121-41.

185. The Declaration of Helsinki outlines recommendations for biomedical research involving human subjects. Sharona Hoffman, *The Use of Placebos in Clinical Trials: Responsible Research or Unethical Practice*, 33 CONN. L. REV. 449, 474-75 (2001). Adopted by the Eighteenth World Medical Association General Assembly at Helsinki, Finland in 1964, it was revised again in 1975,

and eloquent ethical codes concerning human experimentation.<sup>187</sup> In order to promote adherence to ethics, IRBs are instructed to assess risks, ensuring that they are reasonable in light of the benefits<sup>188</sup> and have been minimized by sound research design,<sup>189</sup> that selection of subjects is equitable, care has been taken to protect vulnerable populations,<sup>190</sup> and legally effective informed consent has been obtained<sup>191</sup> prior to approving the research on human subjects. In particular, IRBs are required to provide heightened protection to certain groups, "when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons."<sup>192</sup> The regulations address in detail the special protections afforded to research involving children,<sup>193</sup> prisoners,<sup>194</sup> as well as pregnant women and in vitro fertilization.<sup>195</sup>

#### IV. THE IRBS' ROLE IN RECENT HUMAN SUBJECT RESEARCH GONE AWRY

A number of other well-publicized incidents occurring in the past two or three years have demonstrated the flaws in the current system. These studies have shaken public confidence in human subject research and, in each, criticism was lodged against local IRBs as well as research-

---

1983, 1989, 1996, and 2000. *Id.* at 474. It demands that experimental procedures must be independently reviewed, conform to generally accepted scientific principals, hazards be identified, predicted and weighed against the benefits, and that the subject's interests "must always prevail over the interests of science and society." World Med. Ass'n, Declaration of Helsinki, 1964, as amended by WMA 48th General Assembly, Somerset West, South Africa, Oct. 1996, available at [www.wma.net/e/policy/17c.pdf](http://www.wma.net/e/policy/17c.pdf), at 1-5.

186. The Belmont report was commissioned in 1974 and first published under the National Research Act of 1979. Department of Health, Education & Welfare, *Belmont Report: Ethical Principles & Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*, 44 Fed. Reg. 23,192 (Apr. 18, 1979). It identified respect for persons, beneficence, and justice as three basic ethical principles relevant to research involving human subjects. *Id.* at 23,193-94. Application of these principles is achieved through informed consent, the careful assessment of risks and benefits, and the proper selection of subjects. *Id.* at 23,195-96; see also Hoffman, *supra* note 185, at 472-74 (discussing the Belmont Report).

187. See Richard Delgado & Helen Leskovic, *Informed Consent in Human Experimentations: Bridging the Gap Between Ethical Thought and Current Practice*, 34 UCLA L. REV. 67, 71 n.14 (1986); see also National Institutes of Health, *Historical, Ethical, and Legal Foundations for the NIH's Policies and Procedures*, available at [http://ohsr.od.nih.gov/guidelines.php3#x\\_app1](http://ohsr.od.nih.gov/guidelines.php3#x_app1) (last modified Mar. 2, 1995).

188. 45 C.F.R. § 46.111 (a)(2).

189. 45 C.F.R. § 46.111 (a)(1).

190. 45 C.F.R. § 46.111 (a)(3).

191. 45 C.F.R. § 46.111 (a)(4).

192. 45 C.F.R. § 46.111 (b).

193. 45 C.F.R. §§ 46.401-409.

194. 45 C.F.R. §§ 46.301-306.

195. 45 C.F.R. §§ 46.201-211.

ers.<sup>196</sup> These events include the death of Jesse Gelsinger, an eighteen-year-old volunteer with an inherited liver disorder, who died during a gene therapy experiment at the University of Pennsylvania;<sup>197</sup> allegations that as many as twenty participants in a study conducted at the Fred Hutchinson Cancer Center may have died unnecessarily during the course of a twelve-year-long cancer treatment study because scientists ignored clear evidence that the treatment did not work and actually harmed subjects;<sup>198</sup> and the death of twenty-four-year-old Ellen Roche, a healthy research volunteer who died within days of inhaling an unapproved drug used to induce asthma-like symptoms.<sup>199</sup> Though these incidents have recently drawn national attention to the issue of human subject research, they are by no means isolated events.<sup>200</sup> Indeed, some suggest that these incidents occur more frequently than believed and that they result from fundamental failures in the system designed to protect human subjects. Lawsuits in these cases may invite more courts to examine the national system of human subject protections and prompt changes.

In 2001, the *Seattle Times* published a five-part investigative report describing "Protocol 126," a blood cancer experiment conducted over a twelve-year period in the 1980s and 1990s at the premier Fred Hutchinson Cancer Research Center.<sup>201</sup> The *Seattle Times* reported that perhaps as many as twenty subjects likely died prematurely as a result of the failed experiment that continued despite evidence that the protocol did not work and was leading to premature deaths.<sup>202</sup> According to the *Seat-*

---

196. See Anderlik & Elster, *supra* note 1, at 220-25 (discussing these recent incidents and potential IRB member liability).

197. See *infra* notes 214-235 and accompanying text.

198. See *infra* notes 201-213 and accompanying text.

199. See *infra* notes 236-255 and accompanying text.

200. Other adverse events drawing public attention include: the death of Gage Stewart, an infant suffering gastroesophageal reflux disorder, at a pharmaceutical clinical trial of two drugs at Children's Hospital in Pittsburgh, Pennsylvania; the death of three-year-old Tyler Shelton at the University of Arkansas Children's Hospital during a clinical trial on treatment of kidney cancer after improper cancer staging; and the death of healthy Nicole Wan, age nineteen, at the University of Rochester, following administration of a toxic dose of lidocaine during an experiment on the effects of smoking and air pollution. See Sharon Begley & Donna Foote, *Trials and Errors*, NEWS & OBSERVER, RALEIGH, NORTH CAROLINA, Sept. 9, 2001, at A25, available at A252001 WL 3481841. Historical accounts of human subject research abuses include: LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH, 69-72 (2d ed. 1988); THE NAZI DOCTORS, *supra* note 133; see also Katz, *supra* note 165 (providing historical details of numerous notorious cases throughout history).

201. Duff Wilson & David Heath, *Uninformed Consent, What Patients at "The Hutch" Weren't Told About the Experiments in Which They Died*, SEATTLE TIMES, March 11-15, 2001, available at [http://seattletimes.nwsources.com/uniformed\\_consent/](http://seattletimes.nwsources.com/uniformed_consent/) [hereinafter SEATTLE TIMES]. This site is a repository for the initial five articles, supporting documents, responses from Fred Hutchinson Cancer Research Center, and other links; see also Anderlik & Elster, *supra* note 1, 221-22 (2001) (describing events leading to the filing of the lawsuit).

202. SEATTLE TIMES, *Blood Cancer Experiment*, *supra* note 201. The protocol was designed to determine whether using monoclonal antibodies to kill T-cells during bone marrow transplants would reduce graft-versus-host disease, an immune reaction to transplants that had a five to ten percent mortality rate. *Id.* The protocol was first rejected by the IRB because of concerns that there

*the Times*, various entities were to blame. It condemned the principal investigators who ignored the mortality rates that exceeded conventional treatment.<sup>203</sup> It explained that perhaps the investigators and Fred Hutchinson were motivated by their own financial interests in Genetic Systems, a company that held a financial stake in the antibodies developed to diagnose or treat infectious disease and cancer.<sup>204</sup> This information was not revealed to the patients or the IRB.<sup>205</sup> Though the IRB inquired into the possible financial conflicts of interests among the researchers with a financial stake in the success of the protocol, the researchers denied the conflict and the IRB failed to pursue a fuller investigation.<sup>206</sup> More revealing of systemic failure, the *Seattle Times* blamed the center's IRB as well as the external agencies tasked with oversight of the study.<sup>207</sup> These entities allegedly failed in their singular responsibility to protect the human subjects from ill-conceived or unreasonably dangerous experimentation.<sup>208</sup> Moreover, Fred Hutchinson's IRB allegedly failed to exercise independent leadership and oversight, and thereby failed to perform the duties mandated by federal law.<sup>209</sup> For example, the *Seattle Times* pointed to instances where the IRB's concerns were ignored,<sup>210</sup> it

---

had been inadequate animal studies, that the subject population was actually among a group that was not at great risk for GVHD and would enjoy a more favorable outcome under conventional treatment than others, the lack of FDA approval for the use of the experimental agent, and inadequate warning in the informed consent about survival statistics for GVHD generally. *Id.* These concerns were not addressed and the protocol was approved with different reviewers at a subsequent meeting. *Id.*

As the study progressed, one of the antibodies became associated with unexpected new cancers in subjects and the subject participants had a higher rejection and recurrent malignancy rate than did conventional patients. *Id.* By 1984, researchers acknowledged an unusually high graft failure rate in their study subjects, but they did not end the trial, even though, at their own institution, other clinical trials with untreated marrow were enjoying better and better success rates. SEATTLE TIMES, *Blood Cancer Experiment*, *supra* note 201. In fact, as the failures mounted, the IRB approved Protocol 126 changes, even though each yielded no better result. *Id.* Furthermore, mounting evidence suggested that with Protocol 126 the "relapse risk 2.5 years post-transplant was 100 percent . . . as compared with 25 percent in patients administered unmodified marrow." *Id.* In sum, "the experiment was almost uniformly fatal." *Id.*

The experiment quietly ended in 1993 and the results were never reported. *Id.* The story came to light through the tenacious efforts of Dr. John Pesando, a former employee and physician, who over two decades first complained from within and then later wrote endless letters to federal and state agencies and the media trying to get someone to take notice that human subjects were dying needlessly with little success until the *Seattle Times* took up the story in 2001. SEATTLE TIMES, *The Whistleblower*, *supra* note 201.

203. SEATTLE TIMES, *Blood Cancer Experiment*, *supra* note 201.

204. SEATTLE TIMES, *The Whistleblower*, *supra* note 201.

205. SEATTLE TIMES, *Blood Cancer Experiment*, *supra* note 201.

206. *Id.* In fact, Fred Hutchinson Cancer Center promulgated a conflict of interest policy in 1983, which, after examining filings with the Securities and Exchange Commission, the *Seattle Times* reported were violated. *Id.*

207. *Id.*

208. *Id.*

209. SEATTLE TIMES, *Blood Cancer Experiment*, *supra* note 201.

210. *Id.* For example, the initial protocol was rejected but was resubmitted and subsequently approved without addressing the detailed criticisms that the first IRB raised. *Id.* The IRB questioned the controls on antibody use, especially whether there had been adequate animal testing

approved protocol changes with only a perfunctory review, and most alarmingly, where the criticism voiced by IRB members within the institution was chilled through intimidation.<sup>211</sup> The lead researcher chastised the IRB when he stated that in addition to the IRB members' responsibility to review the ethical considerations of the study, they were also required to assist the researchers and not hinder the research.<sup>212</sup> As a result of these alleged deficiencies, the families of the subjects who died filed a class action lawsuit which is currently pending.<sup>213</sup>

Recently, the University of Pennsylvania also became embroiled in a public controversy arising out of human subject experimentation. In September 1999, eighteen-year-old Jesse Gelsinger died while participating in a University of Pennsylvania Phase I clinical trial testing a new gene therapy treatment for ornithine transcarbamylase ("OTC") deficiency, a rare, genetic liver disorder.<sup>214</sup> Although many individuals with OTC die in infancy, Gelsinger, suffering from a milder form, was able to manage it with a low protein diet supplemented by medication.<sup>215</sup> Gelsinger's physicians recommended the gene therapy trial conducted at the University of Pennsylvania, and eight days after the infusion of a genetically altered virus by the researchers, Gelsinger died.<sup>216</sup> His father reported that he and his son believed that the experimental procedures offered therapeutic potential.<sup>217</sup> In the words of one commentator, however,

---

without effect. *Id.* In 1983-84, the IRB was particularly active in voicing concern and trying to get answers. The IRB asked to set up an independent review "to consider the merits of all the monoclonal antibodies under study" and sought guidance from the National Institute of Health to no avail. *Id.* The center refused to initiate an outside review. SEATTLE TIMES, *Blood Cancer Experiment*, *supra* note 201.

211. SEATTLE TIMES, *Blood Cancer Experiment*, *supra* note 201 (explaining that IRB members "felt unable to do a proper scientific assessment of Protocol 126. They didn't have the information or the power to their job"). One victory for the IRB was to effect a change in the protocol so that that the "lowest risk patients"—those who enjoyed a good survival chance with other therapy—were excluded from the study. *Id.*

212. *Id.*

213. Lorraine Anastasia Lezama, *Research Guidelines: Lawsuit Filed Against Cancer Center*, 29 J.L. MED. & ETHICS 231, 231-32 (2001) (describing the allegations). The class action suit was filed by the law offices of Sherman, Silverstein, Kohl, Rose & Podolsky, which is the same firm that represented Jesse Gelsinger's estate in the suit against the University of Pennsylvania. *Class Action Suit Against Fred Hutchinson Cancer Center Sends Shock Waves Through Clinical Trials Community*, available at <http://www.sskrplaw.com/publications/010412.html>.

214. See generally Anderlik & Elster, *supra* note 1, at 220-21 (describing and discussing the protocol); Barker, *supra* note 136, at 615-19 (same).

215. Barker, *supra* note 136, at 616.

216. A number of sources detail the experiment and his death. See, e.g., Barker, *supra* note 136, at 615-17; Tim Beardsley, *Gene Therapy Setback*, SCI. AM. (Feb. 2000), available at <http://www.sciam.com/2000/0200issue/0200techbus5.html>; Michael Baram, *Making Clinical Trials Safer for Human Subjects*, 27 AM. J.L. & MED. 253, 255-57 (2001); Sherman, Silverstein, Kohl, Rose & Podolsky Law Offices, *Jesse's Intent*, available at <http://www.sskrplaw.com/gene/jessieintent.html> (last visited June 14, 2002) (providing Gelsinger's father's description of his son's decision to enter the study and following him through his last days).

217. Barker, *supra* note 136, at 619. This is borne out by the determination letter issued by OHRP, which stated that OHRP was concerned that the informed consent documents reviewed and

"there was virtually no chance that the experiment—which researchers insisted on calling a *therapy* trial—would provide him with any therapeutic benefit."<sup>218</sup> The study intended to evaluate the safety of the procedure, rather than the treatment's effectiveness.<sup>219</sup> The possibility of improvement from this study was overstated, whereas the risks were understated in the consent form.<sup>220</sup> Moreover, the Gelsingers were not informed that "at the time the study commenced, in more than 390 clinical trials of gene therapy in the last decade, no one had ever been cured,"<sup>221</sup> and in addition, the consent form failed to "disclose that in earlier versions of the same experiments on monkeys, the monkeys had died."<sup>222</sup>

Reportedly, evidence suggested that there were earlier problems and that the studies were not yielding favorable results. Of the seventeen patients treated prior to Gelsinger, only three showed any sign of improvement or benefit.<sup>223</sup> Moreover, the virus given to Gelsinger "spread far beyond his liver, where it was supposed to correct the defect in his cells. Within the liver it had bound to immune cells far more than to the hepatocytes it was meant to target."<sup>224</sup> In addition, Gelsinger's attorneys alleged that the researchers may have had substantial conflicts of interest due to their financial interests in the company that owned the product being tested.<sup>225</sup> These interests went undisclosed to the participants in the

---

approved by the IRB for the OTCD study may have failed to address several elements such as an explanation of the purposes of the research. University of Pennsylvania Determination Letter, May 7, 2001, 3-4, available at [http://ohrp.osophs.dhhs.gov/detrm\\_lettrs/may01a.pdf](http://ohrp.osophs.dhhs.gov/detrm_lettrs/may01a.pdf). [hereinafter University of Pennsylvania, Determination Letter]. The consent documents' language suggests that "the investigators knew what would happen in the trial." *Id.* at 4. Finally, "the informed consent documents refer to it as 'therapy' when there [was] no knowledge that this Phase I trial would be therapeutic." *Id.*

218. Barker, *supra* note 136, at 616; see also University of Pennsylvania, Determination Letter, *supra* note 217, at 4.

219. Barker, *supra* note 136, at 616.

220. The Determination Letter commented:

The informed consent document stated "by giving the virus directly into the right side of the liver, we hope to obtain the maximal effect of the gene in the liver and to keep to a minimum any exposure of left-sided liver cells and non-liver cells to the virus." There was no evidence from animal studies that this was the case. The revised grant application submitted to FDA in March of 1998 stated that biopsies of baboons transduced with the second generation vector via the hepatic artery showed liver toxicity in the targeted and non-targeted lobes of the liver.

University of Pennsylvania, Determination Letter, *supra* note 217, at 4.

221. Barker, *supra* note 136, at 616-17.

222. *Id.* at 617.

223. Beardsley, *supra* note 216.

224. *Id.*; see also Barker, *supra* note 136, at 617 ("When four other patients in the trial experienced elevated liver enzymes, the researchers should have stopped the trial immediately, notified both the University's Institutional Review Board and two federal regulatory agencies, and revised the consent form.").

225. Gelsinger v. University of Pennsylvania, Complaint, available at <http://www.sskrplaw.com/links/healthcare2.html> (last visited June 14, 2002); see also Anderlik & Elster, *supra* note 1, at 220; Frances H. Miller, *Trusting Doctors: Tricky Business When It Comes to Clinical Research*, 81 B.U. L. REV. 423, 426 (2001).

study.<sup>226</sup>

The University of Pennsylvania launched an extensive, independent evaluation of its gene therapy and human subject research procedures.<sup>227</sup> In addition, it voluntarily instituted reforms.<sup>228</sup> For example, the University decided to review and strengthen its IRB system, and in particular, it created an IRB consisting of members with special expertise to evaluate gene therapy protocols.<sup>229</sup> Following an investigation, the Office for Human Research Protections issued a determination letter to the University of Pennsylvania.<sup>230</sup> The letter criticized the manner in which the research was conducted, focusing on deviations from the protocol's exclusion criteria, the failure to promptly report adverse events, and the modification of the protocol without prior IRB approval.<sup>231</sup> It also raised issues concerning particular IRB deficiencies, including a lack of sufficient information when reviewing a protocol revision, approval of an inadequate informed consent document which erroneously implied that the study and procedures were therapeutic, failure to require amendments to the consent form to comply with the revisions in the protocol, and the inadequate description of the foreseeable risks in light of prior animal studies.<sup>232</sup>

Gelsinger's estate filed suit against the researchers, the university and its officials, including the bioethicist who advised the project.<sup>233</sup> The suit alleged that the researchers failed to obtain informed consent, concealed prior adverse events, and failed to disclose that the institution and the director of the gene therapy institute would profit from the school's discovery because both had a financial interest in the company that sponsored the gene research.<sup>234</sup> The Gelsinger family settled the suit with the

---

226. Gelsinger Complaint, *supra* note 225.

227. See The Institute for Human Gene Therapy, *University of Pennsylvania Announces Actions, available at* <http://www.uphs.upenn.edu/ihgt/upennacts.html> (May 24, 2001).

228. *Id.* The school commissioned William Danforth to serve as its chair and asked the committee to recommend actions to increase human subject protection. See Eugene Russo, *Penn Restructures Gene Therapy Institute*, THE SCIENTIST, (June 12, 2000), *available at* [http://www.the-scientist.com/yr2000/jun/russo\\_p12\\_000612.html](http://www.the-scientist.com/yr2000/jun/russo_p12_000612.html).

229. See *supra* note 227.

230. See University of Pennsylvania, Determination Letter, *supra* note 217.

231. *Id.* at 2-7.

232. *Id.*

233. Anderlik & Elster, *supra* note 1, at 220. Notably, the bioethicist, Caplan, advised researchers that it would be unethical to perform the experiments on terminally ill infants because neither they nor their distraught parents could give adequate informed consent. Arthur Allen, *Bioethics Comes of Age*, SALON MAGAZINE, Sept. 28, 2001, *available at* <http://www.salon.com/health/feature/2000/09/28/caplan/index1.html>. Thus, the research emphasis switched to adults who, like Gelsinger, were not as sick. *Id.* That decision drew criticism. One commentator criticized that Caplan's advice may meet the criteria of informed consent, but it defies common sense. *Id.* "When you're about to test a speculative and potentially dangerous medical intervention, you try to do it on people who are unlikely to be worse off than if they hadn't undergone the intervention." *Id.* The experiment should have been conducted on terminally ill babies, not Gelsinger, who had his condition under control before entering the trial. *Id.*

234. See Gelsinger Complaint, *supra* note 225.

University of Pennsylvania.<sup>235</sup>

On June 3, 2001, Ellen Roche, a healthy volunteer, died following her participation in an asthma study conducted by Johns Hopkins University.<sup>236</sup> As a participant in the study, Roche inhaled hexamethonium, a substance that has not been "approved by the FDA for use in humans, and has never been approved by the FDA for administration via inhalation."<sup>237</sup> The ensuing federal investigation required Johns Hopkins to immediately suspend all federally funded research, with limited exceptions, until specific corrective actions were taken.<sup>238</sup>

As with the Protocol 126 and Gelsinger incidents, critics claimed the IRB was partly responsible.<sup>239</sup> The determination letter issued by the OHRP noted the IRB's failure to adequately review the experiment, and particularly to evaluate the use of hexamethonium.<sup>240</sup> The IRB neglected to acquire literature, "available [through] routine MEDLINE and Internet database searches," on the known lung toxicity of hexamethonium.<sup>241</sup> It also "failed to obtain sufficient information regarding the source, purity, quality, and method of preparation and delivery of the hexamethonium used in the research."<sup>242</sup> OHRP also criticized the IRB's approval of an informed consent document that, among other shortcomings, "failed to adequately describe the research procedures" and the "reasonably foreseeable risks and discomforts."<sup>243</sup> Remarkably, OHRP also determined that the IRB neglected to review research at a convened meeting.<sup>244</sup>

External reviewers commissioned by Johns Hopkins following Roche's death were highly critical of the institution's IRB system as well.<sup>245</sup> The external review committee opined that without primary re-

---

235. See Rick Weiss & Deborah Nelson, *Penn Settles Gene Therapy Suit*, WASH. POST, Nov. 4, 2000, at A4.

236. Lezama, *supra* note 213, at 111; Edith Nichols, *Dark Days at Hopkins*, HOPKINS MEDICAL NEWS (Fall 2001), available at <http://www.hopkinsmedicine.org/hmn/F01/cnews.html> (last visited June 14, 2002). A comprehensive set of documents, including the protocol, correspondence, and critical findings of an external review committee set up in its aftermath are available at <http://www.hopkinsmedicine.org/researchvolunteerdeath.html>. These facts are drawn from the July 19, 2001 Division of Compliance Oversight, Department of Health and Human Services, Determination Letter, available at [http://ohrp.osophs.dhhs.gov/detrm\\_ltr/jul01a.pdf](http://ohrp.osophs.dhhs.gov/detrm_ltr/jul01a.pdf) [hereinafter Johns Hopkins, Determination Letter].

237. Johns Hopkins, Determination Letter, *supra* note 236, at 2.

238. *Id.* at 10.

239. See *id.* at 2-4. The researchers' failures were also noted, including failure to promptly report unanticipated problems, using an unapproved drug, and deviating from the protocol without informing the IRB. *Id.*

240. *Id.* at 2.

241. Johns Hopkins, Determination Letter, *supra* note 236, at 2.

242. *Id.* at 3.

243. *Id.* at 4.

244. *Id.* at 3. OHRP determined that "[m]ost protocols are neither individually presented nor discussed at a convened meeting of any IRB." *Id.* at 5.

245. Letter from Samuel Hellman, Chair, External Review Committee, to William R. Brody, President, Johns Hopkins University (August 8, 2001), available at <http://www.hopkinsmedicine.org/external.pdf>.



viewers, the IRB could not be assured that any member thoroughly reviewed protocols.<sup>246</sup> Moreover, it concluded that the Johns Hopkins system “limits, by its design, active discussion by the full committee, and loses the expertise that committee members bring to review.”<sup>247</sup> It chastised the committee for not transcribing minutes for the previous eighteen months.<sup>248</sup> Of Johns Hopkins arrogance, they wrote, “In spite of the previous review by OHRP whose conclusions mirrored many of our concerns, Johns Hopkins vigorously defended the current practices during our visit.”<sup>249</sup> They criticized an institutional culture that viewed oversight and review as impediments to research.<sup>250</sup> Of the IRB generally, the external committee wrote:

The protocol review process is grossly inadequate and does not conform to current standards. Most importantly, there is no required discussion by the whole IRB of each proposal. Indeed, there was no such discussion of Dr. Togias’ proposal. The minutes were not transcribed in a timely fashion so as to permit their use in preparing the letter to the PI. At the time of the writing of this report they are still not available.<sup>251</sup>

In response to the findings by OHRP and the external reviewers, in February 2002, Johns Hopkins published what OHRP described as “an honest and insightful examination [that] is very useful to share with the entire research community, as it sends an important message about changing institutional culture in protecting human research subjects.”<sup>252</sup> Johns Hopkins acknowledged the former deficiencies in the IRB system, including an inhuman workload, an eighteen-month backlog in transcription of IRB minutes, its absence of serious discussion in IRB meetings about protocols, and a lack of focus on ethics.<sup>253</sup> The article also detailed broad reforms aimed at creating cultural change that engages researchers as well as the entire institution in thoughtful ethical evaluation of research projects.<sup>254</sup> Johns Hopkins also explained that it intended to increase the number of IRBs as well as the resources for IRB review, engage in extensive training for researchers and IRB members, and impose

---

246. *Id.*

247. *Id.*

248. *Id.*

249. *Id.*

250. *See supra* note 245.

251. *Id.*

252. Email from OHRP (on file with the author) (acknowledging the Johns Hopkins article and encouraging it to be widely disseminated and recommended to the entire research community).

253. *See* Dale Keiger & Sue De Pasquale, *Trials and Tribulations*, *JOHNS HOPKINS MAGAZINE*, Feb. 2002, available at <http://www.jhu.edu/~jhumag/0202web/trials.html>.

254. *Id.*

penalties on those who fail to comply with the system.<sup>255</sup>

## V. WHY IRBS FAIL TO PROTECT HUMAN SUBJECTS

As many commentators have acknowledged, IRBs are often too weak, overburdened, ignorant, or conflicted to adequately perform the important duties assigned to them by the federal system. The weaknesses in the IRB system are pervasive, and the resulting widely publicized gaffes should come as no surprise. Importantly, these deficiencies jeopardize the effectiveness of the federal system that relies heavily on IRBs to safeguard human subject research. Under federal regulations, the 3,000-5,000 local IRBs act as the gatekeepers standing between the researcher and her research.<sup>256</sup> Remarkably, in spite of all the elaborate rules it promulgated, the federal government barely oversees the IRB system in order to ensure that it complies with its regulations.<sup>257</sup> Expenditures on human subject protection are woefully inadequate.<sup>258</sup> For example, "the National Institutes of Health spent less than 0.5 percent of its human research budget last year on activities aimed at protecting patients."<sup>259</sup>

In 1998, the Office of Inspector General issued a comprehensive report warning that "[t]he effectiveness of IRBs is in jeopardy."<sup>260</sup> In particular, it found that changes in the nature and number of research proposals have strained the IRB system, and thus, they review "too much, too quickly, with too little expertise."<sup>261</sup> Moreover, the Inspector General criticized that continuing review of projects is scant, IRB independence is threatened by conflicts, and members have too little training to perform their duties.<sup>262</sup> Finally, the Inspector General complained that the effectiveness of the IRB system has not been subjected to critical evalua-

---

255. *Id.*

256. There are approximately 3-5,000 IRBs across the country, in hospitals, universities, state and federal government agencies, and nonprofit and for-profit entities where research involving human subjects occurs. See Department of Health and Human Services, Office of Inspector General, *Institutional Review Boards: Their Role in Reviewing Approved Research*, 3, available at <http://oig.hhs.gov/oei/reports/a273.pdf> (June 1998) [hereinafter Inspector General, *Reviewing Approved Research*].

257. See 45 C.F.R. § 46.103 (5); Goldner, *supra* note 175, at 99-100 ("Apart from this negotiated assurance process and these requirements for reporting violations, there is no other formal mechanism whereby the activities of IRBs are in any way monitored by the federal government."); Inspector General, *Reviewing Approved Research*, *supra* note 256, at iii ("The OPRR Oversight focuses on upfront assurances. Only rarely does its oversight involve on-site assessments of IRB performance.").

258. Jacob M. Appel, *Research Guidelines: Changes Urged*, 29 J.L. MED. & ETHICS 103, 104 (2001).

259. *Id.* (noting similarly scant expenditures on human subject protections in the private sector).

260. Inspector General, *Time for Reform*, *supra* note 165, at 4.

261. *Id.* at 5.

262. *Id.*

tion,<sup>263</sup> and “[t]oo much . . . attention now focuses on perfunctory review responsibilities yielding little protective value.”<sup>264</sup>

Without a doubt, IRBs are overworked. Scientists conduct thousands of studies across the United States at any given time,<sup>265</sup> and researchers estimate that as many as 19 million individuals participate in human subject research each year.<sup>266</sup> According to the Inspector General, “IRBs across the country are inundated with protocols,” and the workload of the average IRB has increased to the point that they are unable to provide meaningful review.<sup>267</sup> As a result, some IRBs provide “only one to two minutes of review per study.”<sup>268</sup> The rule requiring each institution to review study protocols conducted in its institution, even when the research is being conducted at many research sites, constitutes one source of overload.<sup>269</sup> This process slows research, frustrates researchers, and unnecessarily taxes an already overburdened IRB system.<sup>270</sup> IRBs expend “scarce resources on reviewing the same protocol that, in some cases, is being reviewed by hundreds of other IRBs, even when overall design and methods can only be changed with great difficulty.”<sup>271</sup>

In addition to being overburdened, IRB members are neither sufficiently trained in the substantive topic of ethical research conducted on human subjects, including issues of research design and informed consent, nor in the morass of federal requirements that guide the review process.<sup>272</sup> Both the Inspector General and the National Bioethics Advisory Commission (NBAC) cited increased need for education of IRB members and recognized a shared obligation at the federal and at the institutional level.<sup>273</sup> In its 2001 final report, NBAC explained that “[d]espite this enduring recognition of the important role of education, the educational function of the oversight system has been only minimally implemented through federal programs.”<sup>274</sup> This failure to emphasize

---

263. *Id.*

264. *Id.* at 11.

265. See Adil E. Shamoo, *Adverse Events Reporting—The Tip of an Iceberg*, 8 ACCOUNTABILITY IN RESEARCH 197, 206 (2001) [hereinafter Shamoo, *Adverse Events Reporting*]. The National Institute of Health alone funded over 4,000 clinical trials and other research projects in 1997. *Id.* Johns Hopkins acknowledged that its two IRBs were reviewing approximately 80 protocols per month of “30 to 90 pages of highly technical material” and that “the volume of protocols overwhelmed the system.” Keiger & De Pasquale, *supra* note 253.

266. Shamoo, *Adverse Events Reporting*, *supra* note 265, at 207. That number includes the 7 million known human subjects participating in National Institute of Health (NIH) funded studies as well as other governmental agencies funding human subject research and private research conducted by pharmaceutical companies and others. *Id.* at 207-08.

267. Inspector General, *Time for Reform*, *supra* note 165, at 5.

268. *Id.*

269. See *id.* at 10.

270. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 117.

271. *Id.* at 118.

272. See Inspector General, *Time for Reform*, *supra* note 165, at 8.

273. *Id.*; see also NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 45-46.

274. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 46.

education "at the federal level was repeated at the local level, with institutions often failing to provide educational programs to their investigators, research staff, and IRB members."<sup>275</sup> According to a 1995 survey, one-quarter of IRBs at universities "offered no training at all to their members" and a "vast majority" offered fewer than four hours of training to IRB members.<sup>276</sup> This lack of training constitutes a fundamental flaw and is problematic because it "impedes [independent IRB members'] ability to serve as an effective counterbalance to institutional and scientific interests."<sup>277</sup>

IRB education in ethics is particularly essential because there is no assurance that principal investigators and scientists have necessarily received training on ethical human subject research. In October 2000, for the first time, the National Institutes of Health (NIH) instituted a rule requiring all investigators submitting NIH applications to receive education in human subject protection.<sup>278</sup> Although institutions may develop their own training programs, the NIH facilitates education by offering an online tutorial, initially developed for the NIH staff.<sup>279</sup> Aside from that development, one cannot assume that the thousands of researchers in a variety of academic fields have received any training in the ethics of human subject research in the course of their education or otherwise.

The federal system is complex and this complexity presents its own obstacles to meaningful review.<sup>280</sup> In addition to the actual regulations, there are dozens of Dear Colleague letters<sup>281</sup> and Guidance Letters<sup>282</sup> covering topics ranging from the circumstances under which an IRB can convene a meeting by telephone,<sup>283</sup> to how an IRB can ensure informed consent to the non-English speaking subjects.<sup>284</sup> IRBs are also required to

---

275. *Id.* NBAC noted that a lack of knowledge about procedures and ethical principles were chief among the deficiencies identified in audits and suspensions and further commented that IRB chairs and members strongly supported increased education. *Id.*

276. Inspector General, *Time for Reform*, *supra* note 165, at 8 (citing Gregory J. Hayes et al., *A Survey of University Institutional Review Boards: Characteristics, Policies, and Procedures*, IRB, May-June 1995, at 1-6).

277. *Id.*

278. See National Institutes of Health, *Required Education in the Protection of Human Research Participants*, (June 5, 2000 as revised August 25, 2000), available at <http://grants1.nih.gov/grants/guide/notice-files/NOT-0D-00-039.html> (last visited June 14, 2002).

279. *Id.* The tutorial is available at [http://ohsr.od.nih.gov/irb\\_cbt/](http://ohsr.od.nih.gov/irb_cbt/) (last visited June 14, 2002); see also National Institutes of Health, Office of Extramural Research, *Frequently Asked Questions for the Requirement for Education on the Protection of Human Subjects*, available at [http://grants2.nih.gov/grants/policy/hs\\_educ\\_fa\\_q.htm](http://grants2.nih.gov/grants/policy/hs_educ_fa_q.htm) (last modified May 8, 2002).

280. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 14.

281. Office for Human Research Protections, Department of Health and Human Services, available at <http://ohrp.osophs.dhhs.gov/dearcoll.htm> (last modified June 21, 2001).

282. Office for Human Research Protections, Department of Health and Human Services, available at <http://ohrp.osophs.dhhs.gov/g-topics.htm> (last modified May 3, 2002).

283. Office for Human Research Protections, Department of Health and Human Services, available at <http://ohrp.osophs.dhhs.gov/references/irbtel.pdf> (Mar. 28, 2000).

284. Office for Human Research Protections, Department of Health and Human Services, available at <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/ic-non-e.htm> (Nov. 9, 1995).

understand the significant differences between provisions mandated by the Food and Drug Administration, NIH, and the Department of Human Services.<sup>285</sup> As a result of the extensive list of rules, it is not uncommon for IRBs to miscalculate the complexities of the federal regulations.

Overwork has also resulted in IRB failure to adequately fulfill the continuing review obligations. As a result of the increased workload, IRBs have become preoccupied with form over substantively meaningful review of initial protocols, adverse events, and continuing reviews.<sup>286</sup> As one critic stated, "IRBs are spending too much time editing informed-consent forms and too little time analyzing the risks and potential benefits posed by research."<sup>287</sup> In fact, it is widely known that IRBs have long neglected continuing review obligations. Federal regulations require IRBs to undertake continuing review of ongoing research projects at least annually.<sup>288</sup> As the Inspector General noted, however, "[m]any IRBs find that with significant increases in the quantity of new research protocols, they have little time left for annual reviews," and they have focused "much more on complying with procedural requirements than on conducting substantive continuing review."<sup>289</sup>

One facet of continuing review that is often neglected concerns adverse events. Researchers conducting studies with federal support must report adverse events to their own IRB and to the federal government.<sup>290</sup> In spite of this reporting requirement, it is impossible to obtain an accurate count of the number of human subjects that suffer from adverse events each year as a result of their participation in research. One reason the extent of adverse events is unknown is that some research is not subject to federal reporting requirements at all.<sup>291</sup> Underreporting is also a

---

285. See Stuart L. Nightingale, *Challenges in Human Subject Protection*, 50 FOOD & DRUG L.J. 493, 499-500 (1995) (discussing IRB difficulties in understanding competing and differing regulations).

286. Inspector General, *Time for Reform*, *supra* note 165, at 6 (describing a typical IRB agenda as covering 18 initial reviews, 9 expedited reviews, 43 protocol amendments, and 21 adverse-event reports in a 2 ½ hour meeting). NBAC wrote:

The quality of IRB review is often compromised by the burden of excessive paperwork, because although IRBs are broadly charged with ethical review, in practice they also must fulfill many procedural requirements. While some of these requirements are designed to ensure compliance with ethical standards . . . others appear to have little relevance to ethical standards of protection of participants . . . In all of their deliberations, IRBs must keep track of a range of detailed regulations and document the grounds on which they make their decisions in accordance with them.

NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 13-14.

287. Weijer, *supra* note 62, at 344. Weijer further notes that the research literature reflects this preoccupation with the consent form and lack of attention to meaningful review of the research design.

288. 45 C.F.R. § 46.109(e) ("An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and research.").

289. Inspector General, *Reviewing Approved Research*, *supra* note 256, at 7.

290. Shamoo, *Adverse Events Reporting*, *supra* note 265, at 199.

291. *Id.* at 201-02.

problem. Studies indicate that tens of thousands of adverse events as well as thousands of deaths are unreported in violation of federal law.<sup>292</sup> For example, discussing gene therapy, one commentator wryly noted that:

In the past year, researchers in the United States have been "catching up" on their reporting to regulators, and it now appears that at least 691 serious side effects—ranging from high fevers to serious infections and even seizures—have been experienced by experimental subjects in U.S. gene therapy trials using modified adenovirus vectors. Researchers claim that most of these side effects were caused by the subjects' underlying medical conditions, and undoubtedly this is so. Still, of the 691 serious side effects, only thirty-nine were reported—as regulations require—when they happened. The others were reported in the wake of Pennsylvania's program shutting down, no doubt because of fear of the same fate. More than 500 serious side effects were reported just this year, of which 130 occurred in the year 2000. This represents a noncompliance rate of five percent, or put another way, a rate of failure to comply almost ninety-five percent.<sup>293</sup>

Significantly, the adverse effects of hexamethonium on Ellen Roche were not promptly reported,<sup>294</sup> adverse events prior to Gelsinger's death went unreported,<sup>295</sup> and reports on adverse effects on Protocol 126 were allegedly delayed.<sup>296</sup>

As NBAC dolefully noted, even when adverse events are reported, IRB review is a woefully ineffective mechanism for monitoring adverse events.<sup>297</sup> Upon receiving an adverse event report, local IRBs are unable to "determine whether the event is frequent or rare, whether it is caused by their research as opposed to the underlying illness or standard treatment, or whether the adverse event is more common in the intervention group than in the control groups."<sup>298</sup> It is nearly impossible for a committee to discern the significance of adverse events reported to the IRBs across the nation. In essence, it is like "looking for a needle in a haystack."<sup>299</sup> Because they lack access to the necessary information needed

---

292. *Id.* at 214. Dr. Adil Shamoo developed these estimates by examining the number and nature of reported adverse events and deaths in clinical trials and comparing this number with the number of reportable events such as suicide and medical error rates that would predictably occur. *Id.* at 201-11. He concluded that the disparity suggests that "the overall reporting of adverse events . . . lacks any credibility." *Id.* at 213.

293. Barker, *supra* note 136, at 618; *see also* Baram, *supra* note 216, at 280 (noting the flood of reporting activity following Gelsinger's death and identifying reasons for underreporting).

294. *See* Johns Hopkins, Determination Letter, *supra* note 236, at 4.

295. *Id.* at 2-3; Weiss & Nelson, *supra* note 235.

296. *See supra* note 202 and accompanying text.

297. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 114-15.

298. *Id.*

299. Inspector General, *Reviewing Approved Research*, *supra* note 256, at 7.

to evaluate these reports, local IRBs are “not only wasting time attempting to analyze them but are also unable to make use of the data.”<sup>300</sup>

According to the Inspector General, similar to “the continuing review requirement, the Federal intent [underlying the reporting of adverse events requirement] was to foster substantive review. But here, too, the reality has been quite different.”<sup>301</sup> Fearing exposure to liability, sponsors have been increasingly likely to report.<sup>302</sup> As a result, IRBs have become inundated with adverse event reports.<sup>303</sup> In response to these and other gaps in safety monitoring, in 1998 NIH began to require its grantees to design and establish “Data Safety Monitoring Boards” for their clinical trials and to submit a data safety monitoring plan with each grant.<sup>304</sup> These boards have duties distinct from the IRB and involve oversight and monitoring activities as they were intended to supplement, rather than supplant, the IRB system.<sup>305</sup>

The IRB system also suffers from more basic, systemic flaws that cannot be cured by simply easing workloads, fostering more diligence, and educating IRB members. These flaws spring from the interests, biases, and conflicts board members bring with them. Many critics have noted conflicts of interest among researchers, the institution, and IRB members.<sup>306</sup> Those related to the IRB may be the most pernicious because they are more subtle and less easy to cure by regulation and disclosure than the more obvious financial conflicts that taint the institution and its researchers. In suggesting that the IRB may not be the appropriate body to perform continuing reviews, the Inspector General astutely noted that “[t]he IRB process is rooted in trust,”<sup>307</sup> and as a result, it reviews

---

300. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 114-15.

301. Inspector General, *Reviewing Approved Research*, *supra* note 256, at 7.

302. *Id.*

303. *Id.*

304. See *NIH Policy for Data and Safety Monitoring*, (June 10, 1998), available at <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>; *Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials*, (June 5, 2000), available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>; National Institutes of Health, *Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multi-center Clinical Trials*, (June 11, 1999), available at <http://grants.nih.gov/grants/guide/notice-files/not99-107.html> [hereinafter *Guidance on Reporting*].

305. *Guidance on Reporting*, *supra* note 304.

306. See, e.g., Baram, *supra* note 216, at 269-72 (discussing institutional and researcher conflicts); Jesse A. Goldner, *Dealing With Conflicts of Interest in Biomedical Research: IRB Oversight as the Next Best Solution to the Abolitionist Approach*, 28 SYMP. J.L. MED. & ETHICS, 379, 381 (2000) (advocating that IRBs should monitor researcher and institutional conflicts of interest); Peter J. Harrington, *Faculty Conflicts of Interest in an Age of Academic Entrepreneurialism: An Analysis of the Problem, the Law and Selected University Policies*, 27 J.C. & U.L. 775, 782-83 (2001) (discussing researcher financial conflicts in medical research); Miller, *supra* note 225, at 431-39 (discussing researcher conflicts of interest). Universities are becoming increasingly entrepreneurial, teaming with private biotech companies and patenting their discoveries. See Zinner, *supra* note 177 (noting changes in federal law that allow universities to apply for patents developed through federally funded research and resulting academic-private partnerships).

307. Inspector General, *Reviewing Approved Research*, *supra* note 256, at 12.

protocols "in a collegial manner assuming the best of intentions on the part of researchers and sponsors."<sup>308</sup> In fact, IRBs eschew the "watch-dog" role in favor of mutual trust, which "inhibits effective continuing review."<sup>309</sup>

An additional problem plaguing the IRB system results from the fact that typically the membership is dominated by scientists, and therefore, the IRB has an inherent "systematic bias which favors the conduct of research."<sup>310</sup> Current regulations require these bodies to consist of only one member who is unaffiliated with the institution, and one who is not involved in the sciences.<sup>311</sup> No doubt there are competing values at stake in human subject research.<sup>312</sup> The federal government invests in research because of society's core belief in the value of scientific research and discovery.<sup>313</sup> On the other hand, the federal government established the IRB system because it recognized a paramount need to protect human subjects from scientific research abuses.<sup>314</sup> By staffing the IRBs primarily with scientists, the government has failed to mitigate the natural bias of scientists and to accomplish the goals underlying the system.<sup>315</sup>

Because an IRB is charged under federal law with protecting human subjects, and yet established to facilitate research at its institution, the board can succumb to conflicts and bias inherent from the outset. In order to obtain federal research money, institutions convene IRBs, and while the board's purpose is to protect human subjects, it is inescapable that the institution's objective is to comply with federal regulations so to obtain funding.<sup>316</sup>

Collegiality and institutional loyalty may inhibit IRBs from conducting thorough and independent reviews of protocols.<sup>317</sup> Most IRB members are employed as faculty or researchers at the institutions to which

---

308. *Id.*

309. *Id.*

310. Goldner, *supra* note 175, at 106; *see also* Keiger & De Pasquale, *supra* note 253 (complaining that boards have too much interest in protecting their own institutions and less in meaningful review).

311. 45 C.F.R. § 46.107(a). Though only one member is required to be a scientist, members generally must have "professional competence necessary to review specific research," and as a result, they become dominated by scientists. *Id.*

312. Goldner, *supra* note 175, at 106.

313. *Id.*

314. *Id.*

315. *Id.* at 107.

316. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 61. NBAC explained:

Because most institutions have an understandable desire to increase their research activities, institutional IRBs may, themselves, face conflicts of interest. And, even independent IRBs have a strong incentive to consider the interests of their institutional contractors.... Some have suggested that the primary function of IRBs has shifted from protecting the participant to protecting the institution.

*Id.*

317. Katz, *supra* note 165, at 40-41.



the investigators belong.<sup>318</sup> These members realize “when sitting in judgment of a research protocol, that their proposals may soon be subjected to similar scrutiny.”<sup>319</sup> As a result, “it is unlikely that members of IRBs will hold investigators to a standard of disclosure and consent that would protect the subjects of research if doing so would place impediments on the conduct of research and, in turn, affect the well-being of their colleagues in decisive ways.”<sup>320</sup>

In addition to a collegial reticence to disapprove another researcher’s experiments, there may also be outright intimidation and retaliation.<sup>321</sup> For example, in Protocol 126, comments by IRB members complaining about the progress of the experiment were not well received, and the evidence suggests the members paid a professional price.<sup>322</sup> According to the *Seattle Times*, “IRB members felt unable to do a proper scientific assessment of Protocol 126 [and that] they didn’t have the information or the power to do their job.”<sup>323</sup>

## VI. REFORMING THE SYSTEM

The rise of the IRB as the frontline protection of human subjects principally resulted from federal efforts,<sup>324</sup> and reform will have to come from federal forces as well. In April 2000, the Inspector General issued a status report on the implementation of its 1998 recommendations.<sup>325</sup> Although the report indicated that federal investigation and enforcement

---

318. *Id.*

319. *Id.* at 41.

320. *Id.*; see also Inspector General, *Time for Reform*, *supra* note 165, at 18 (commenting on methods to improve the ability of the IRB to act independently without pressure or “regard for business concerns”).

321. See Shamoo, *Conflict of Interest*, *supra* note 165, at 207 (quoting 1996 unidentified GAO report) (noting that IRB employees in the same institution may be compromised by collegial ties and institutional pressures to attract and retain funding, reluctance to criticize studies by leading scientists, and their own financial interests in research). In the bleak words of another commentator:

[E]ffective institutional oversight and self-regulation of trial management is highly dependent on the values and behavior of principal investigators, and the capacity and diligence of IRBs. Other studies and investigations confirm this and provide additional evidence of investigator misbehaviors and the ineffectiveness of their IRBs. As a result, it is now widely accepted that IRBs are overwhelmed by trial oversight responsibilities and documentation, are easily misled or ignored by researchers, and are unwilling to challenge institutional colleagues.

Baram, *supra* note 216, at 267-68.

322. See SEATTLE TIMES, *Blood Cancer Experiment*, *supra* note 201. When the IRB initially questioned conflicts of interest, the researcher responded that the committee members “have not only an obligation to review ethical aspects of this work, but also an obligation to assist us and not impede our research.” *Id.*

323. *Id.*

324. LEVINE, *supra* note 200, at 322 (explaining that “[t]he first federal document requiring committee review” was promulgated in the 1950s and applied to intramural research at NIH).

325. See generally Department of Health and Human Services, Office of the Inspector General, *Protecting Human Research Subjects, Status of Recommendations* (Apr. 2000), available at <http://oig.hhs.gov/oei/reports/a447.pdf>.

activity had increased, few of the reforms had been enacted.<sup>326</sup> The particular reforms that had not been implemented included increased IRB flexibility, greater IRB accountability for results, strengthened continuing review, enactment of educational requirements, IRB isolation from conflicts of interest, reduced workloads, and "reengineering the Federal oversight process."<sup>327</sup>

Changes, however, may be underway. In 1995, President Clinton established the National Bioethics Advisory Commission (NBAC) to consider the rights of human research subjects and to develop recommendations to improve the current system.<sup>328</sup> Their final report reflected three general themes:

First . . . there should be fewer federal regulations and more guidance. Second, [regulations] generally [should] focus attention on research for which participants need the most protection and strive to make the level of protection commensurate with the level of risk involved in the research . . . . Third, the recommendations [should] both increase the scope of regulated research and streamline the process of regulatory compliance.<sup>329</sup>

Education is one of the cornerstones of NBAC's recommendations.<sup>330</sup> It recommended partnership between the government, academic institutions, and professional organizations in order to enhance ethics education among scientists.<sup>331</sup> It also called for formal, mandatory education of IRB members, staff, and officials,<sup>332</sup> as well as the demonstration of individual member competence through certification programs aligned with federal standards and developed by institutions.<sup>333</sup>

In order to promote better accountability and training, NBAC also recommended that the federal government facilitate the development of accrediting bodies, establish guidelines used to approve those bodies, and then to encourage institutions to become accredited in order to secure adherence to federal standards and appropriate oversight.<sup>334</sup> Private accreditation by federally approved bodies may establish an effective method to ensure that the inordinately large and diverse institutions now

---

326. See generally *id.*

327. *Id.* at 3.

328. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at xi. The Committee was established by Executive Order 12975 (Oct. 3, 1995) to identify broad principles to govern the ethical conduct of research and to give advice and recommendation to the National Science and Technology Council. *Id.* at Title Page.

329. *Id.* at xi.

330. *Id.* at 45.

331. *Id.* at 48.

332. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 48.

333. *Id.* at 48-49.

334. *Id.* at 49-50.

receiving federal funding are prepared and able to protect human subjects.<sup>335</sup>

Furthermore, NBAC also noted that only a few federal agencies proactively conduct site inspections to ensure institutional compliance with federal regulations.<sup>336</sup> Most inspections result from reported incidents, and therefore, they are conducted solely on a "for cause" basis.<sup>337</sup> Currently, there are no regulations requiring institutions and their IRBs to audit compliance.<sup>338</sup> As a result, NBAC recommended the adoption of "various mechanisms, including assurances of compliance, site inspections, and internal audits."<sup>339</sup>

Of import, there is increasing federal recognition that some entity external to the researcher must monitor compliance and provide oversight continuously, after approval of the research.<sup>340</sup> The scientific community is divided on whether the IRB is appropriate and able to provide that oversight.<sup>341</sup> Some of the problems are evident. "Some argue that as collegial review boards, IRBs should not question the information provided by investigators. On the other hand, others have argued that IRBs should develop mechanisms for continuing review."<sup>342</sup>

NBAC also recommended the creation of clearer federal policies defining institutional, IRB, and researcher conflicts. Acknowledging persistent conflicts of interest that inhibit the IRBs' independence,<sup>343</sup> NBAC called for the promulgation of policies by sponsors and institutions to require disclosure and to manage conflicts of interests.<sup>344</sup> In addition, it also recommended federal policy establishing membership criteria that ensures competence but also that more strongly represents the participant's perspectives by increasing unaffiliated IRB membership at least twenty-five percent.<sup>345</sup>

NBAC also suggested numerous substantive recommendations concerning benefit identification, risk assessment, vulnerability of populations, informed consent and privacy issues.<sup>346</sup> It introduced "research

---

335. *Id.*

336. *See generally id.* at 50-53. These include the FDA, which conducted a limited number of site inspections of IRBs and programs, the Department of Energy, and the Department of Veterans Affairs. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 52-53. The Office of Human Research Protections inspects on a "for cause" basis. *Id.* at 53. OPRR Compliance oversight investigations resulting in restrictions and actions involve many of the most prestigious academic institutions and hospitals in the nation. *See id.* at 54-56.

337. *See* 51-56.

338. *Id.* at 51.

339. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 64.

340. *See generally id.* at 57-64.

341. *See id.* at 57.

342. *Id.*

343. *Id.* at 61.

344. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 64.

345. *Id.*

346. *See generally id.* at 69-108.

equipoise," a term describing "the state in which genuine uncertainty exists regarding which intervention—experimental or control (including placebos)—is better."<sup>347</sup> According to NBAC, "[a] judgment of research equipoise relies on a comparison of the risks and potential benefits of the proposed study interventions with those of accepted practice" and "requires approximate equality in the relation between the risks and potential benefits of the study and control interventions."<sup>348</sup> Explaining how IRBs should assess risks and benefits and calculate the risk-benefit ratio,<sup>349</sup> NBAC urged the adoption of a "component analysis" approach.<sup>350</sup> Under this approach, IRBs are required to consider "each component of a study . . . separately,"<sup>351</sup> and "potential benefits from one component of a study should not be used to justify risks posed by a separate component of a study."<sup>352</sup> This analytic process would have helped the IRB assess the Kennedy Krieger study, where every child gained some indirect benefit but risks were variable depending upon the group to which the child was assigned.<sup>353</sup> Finally, it also encouraged IRBs to consider the vulnerability of particular subjects when balancing the risks and benefits.<sup>354</sup>

As the Inspector General earlier noted, NBAC warned that for the past twenty-five years, oversight through meaningful continuing review of research projects has been virtually nonexistent.<sup>355</sup> It cited overburdened IRBs that are weighed down by the requirement of annual reviews of all projects regardless of their risk as an impediment to meaningful review of risky projects.<sup>356</sup> Importantly, in order to ease some of that burden, NBAC concluded that local review is not sacrosanct, especially in the case of multi-site research.<sup>357</sup> It recommended that federal policy

347. *Id.* at 78.

348. *Id.* (citations and italics omitted).

A variety of intervention-related factors are likely to contribute to the determination of this assessment, including, among others, the relative efficacy of the intervention, the probability and magnitude of side effects, ease of administration, and participant compliance. An experimental intervention may pose greater risk to participants than accepted practice, as long as it also offers the prospect of greater direct benefit to the participant and the relation between the risks and potential benefits falls within a range of equivalency to accepted practice.

NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 78.

349. *Id.* at 69-96.

350. *Id.* at 76.

351. *Id.* at 77.

352. *Id.*

353. See NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 76 (describing Weijer's component approach). To see the approach taken by Weijer, see *Weijer*, *supra* note 62, at 351-52.

354. *Id.* at 92.

355. *Id.* at 112.

356. *Id.* at 112-13.

357. *Id.* at 14. NBAC explained that multi-site research:

[H]as challenged fundamental assumptions about the importance of local review, for the more IRBs duplicate each other's work by reviewing the same protocols, the more pressure there is to show why multiple local reviews of identical research pro-

allow "central or lead" IRB review to ease the duplicative work within the current system.<sup>358</sup> NBAC noted that accrediting IRBs would ensure that regional or central IRB review would still be of sufficient quality.<sup>359</sup> Moreover, while it acknowledged that there could be a potential loss of familiarity with local sensitivities and local knowledge without local review, the federal government should allow IRBs the opportunity to lessen their own role in multi-site and cooperative research.<sup>360</sup> This suggestion alone will be applauded by researchers and sponsors who "are discouraged by having to submit protocols to multiple boards, particularly because changes requested by one board usually have to be approved by the others, a repetitive process that is labor intensive and that can significantly delay research, with little resulting benefit."<sup>361</sup>

Furthermore, NBAC was also troubled that the current regulations do not require researchers to provide compensation for research-related injuries.<sup>362</sup> Rather, the current regulations merely require the informed consent document to explain whether compensation is available for injuries and prohibits the use of legal liability waivers.<sup>363</sup> Therefore, the principle sources of compensation available for injuries resulting from research injuries are the tort system or the participant's private health insurance.<sup>364</sup> NBAC explained that because the public at large reaps the benefits of medical research, it is justifiable to expect the public to fund a national compensation program.<sup>365</sup> NBAC, however, stopped short of

---

protocols are needed. Although local review can provide insight about the social and cultural context of a study . . . IRBs may be squandering precious resources when dozens or hundreds of them must review all aspects of a single, multi-site protocol when the design and methods are unlikely to be changed.

NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 14.

358. *Id.* at 122.

359. *Id.*

360. *Id.*

361. *Id.* at 14.

362. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 123. It explained that "[f]or over 30 years, various parties have discussed alternatives to this option [of resorting to lawsuits for compensation], and many national panels and advisory groups in the United States have recommended the establishment of a compensation program." *Id.* at 124. NBAC noted that the Tuskegee Syphilis Ad Hoc Advisory Panel recommended establishing a "'no fault' clinical research insurance plan" that would compensate injured research subjects without regard to proof of negligence. *Id.* Each proposal has languished and failed. *Id.*

363. 45 C.F.R. § 46.116 (prohibiting "any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence"). The regulation requires research involving more than minimal risk to provide "an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs." 45 C.F.R. § 46.116(a)(6).

364. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 125. Litigation concerning research injuries reveals that the tort system is inadequate to ensure compensation. Litigation is slow and costly and these reasons alone make it an ineffective system to compensate injured research victims. Non-uniform legal standards are applied across jurisdictions. *See generally* Goldner, *supra* note 175, at 70-88 (discussing the effectiveness of the tort system as a normative influence on ethics in research).

365. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 125.

recommending the creation of a compensation system, and instead, it urged the establishment of a federally funded program used to study research injuries as well as the implementation of a pilot study to test compensation mechanisms.<sup>366</sup>

Finally, according to NBAC, the current system contains large and dangerous gaps that have allowed for a large amount of uncontrolled research.<sup>367</sup> It described the existing system as too inflexible to accommodate the variety of research currently conducted and too cumbersome to "react quickly to new developments."<sup>368</sup> While advocating uniformity "across all government agencies, academe, and the private sector," it also called for sufficient flexibility standards "to be applied in widely different research settings or to emerging areas of research."<sup>369</sup> Therefore, NBAC proposed the creation of an "independent oversight office that would have clear authority over all other segments of the federal government and extend protections to the entire private sector for both domestic and international research."<sup>370</sup>

Acknowledging that its proposals would create "additional costs for institutions, sponsors, and the federal government,"<sup>371</sup> NBAC emphasized the importance of reform and called on broad constituencies sharing common interests in reform to work together:

In previous reports, the National Bioethics Advisory Commission (NBAC) recognized that research should not be thwarted because resources are not available to provide the necessary protections for human participants and that compliance would require additional resources . . . . Sponsors of research, whether public or private, should work together with institutions conducting research to make the necessary resources available.<sup>372</sup>

It called for federal appropriations "to carry out the functions of the proposed federal oversight office."<sup>373</sup> In addition, NBAC explained that as research is funded, it will contain "a separate allocation for oversight activities."<sup>374</sup> Finally, it explained that additional federal funding as well as that obtained through other sources should be made available to local institutions in order to operate IRBs and conduct oversight activities.<sup>375</sup>

---

366. *Id.* at 126.

367. *See id.* at 26-28.

368. *Id.* at vi.

369. *Id.*

370. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at vi.

371. *Id.* at 131.

372. *Id.*

373. *Id.* at 133.

374. *Id.*

375. NBAC, ETHICAL AND POLICY ISSUES, *supra* note 11, at 133.

## VI. CONCLUSION

Congress will soon consider these recommendations in earnest as bills are on the near horizon to establish a new National Office of Human Research Protection.<sup>376</sup> The current system resulted largely as a response to past abuses,<sup>377</sup> and predictably, the state of new revelations may eventually yield some improvements in a troubled system. The recent deaths of human subjects participating in research at prestigious institutions across the nation may provide the necessary impetus for a long-needed overhaul of the system.<sup>378</sup> It is small consolation to a family member that someone in his or her family "did not die in vain" and that a person's death or injury in the name of research sparked constructive reform. With regard to recent research related injuries and deaths, there may be some grain of truth to reform springing from the sacrifices of human subjects. Scandals and abuses in human subject research have traditionally served as fuel for change in the system our nation employs to protect human subjects. While no one can dispute the value of human subject research, history has shown us that we cannot neglect our societal role to oversee its conduct. The federal government has awakened to the fact that the current system is outdated, overburdened, and failing to protect subjects as it was intended.<sup>379</sup> The Inspector General and NBAC report have whet the desire to change an unwieldy, broken system that cannot keep pace with the proliferation of research that constantly raises new and difficult ethical challenges. Importantly, the Kennedy Krieger decision heralds the arrival of a new player in human subject research oversight. In *Grimes*, the court established an important judicial role in articulating standards for human subject protection. Given the filing of lawsuits across the nation related to human subject research, judges may provide a strong voice for change in the current deficient system.

---

376. See National Bioethics Advisory's Swan Song, *THE BLUE SHEET*, September 5, 2001, 2001 WL 7811664 (reporting that Representatives Diana DeGette and Jim Greenwood will soon introduce a bill to strengthen human subject research and to establish a National Office for Human Research Oversight); Diana DeGette, *Bioethics Commission to Introduce Patient Protection Bills*, *WASHINGTON DRUG LETTER*, August 6, 2001, 2001 WL 8205327.

377. See, e.g., Childress, *supra* note 165, at 105-06 (discussing the development of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research ("National Commission") in the 1970s to guard against unethical experiments involving human subjects).

378. See *Human Subject Protections Bill Would Create One Federal Oversight Office*, *THE BLUE SHEET*, August 1, 2001, 2001 WL 7811527 (noting that recent lapses in human subject protections should serve "as impetus to pass legislation to improve human subjects protections").

379. See generally NBAC, *ETHICAL AND POLICY ISSUES*, *supra* note 11.

